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1967

I. OXIDATIVE DECARBOXYLATION OF γ-KETOACIDS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

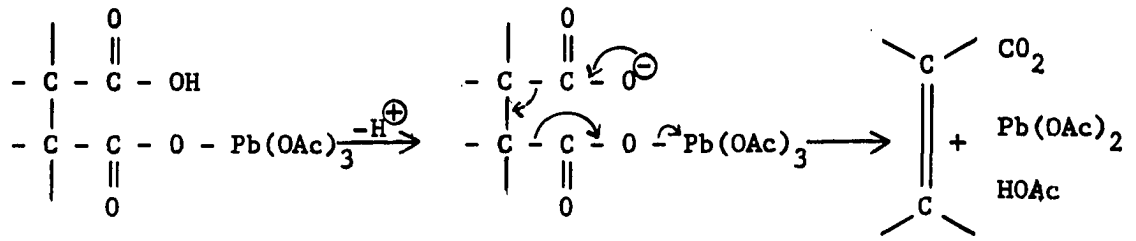
I. LEAD TETRAACETATE DECARBOXYLATION

INTRODUCTION

Lead tetraacetate was first used to cleave 1,2-diols in 1931.[1] Oeda[2] in 1934, using the cleavage of 1,2-diols as an analogy, found that lead tetraacetate would also cleave α-hydroxy acids. In the first practical oxidative bis-decarboxylation of a dicarboxylic acid, the lead (IV) was not employed as the tetraacetate but as the dioxide. Doering[3] refluxed cis-hexahydrophthalic acid with lead dioxide in decalin and was able to isolate cyclohexene in 21% yield. The yields of olefin, when lead dioxide was used, were difficult to reproduce[4] and the reaction could even be explosive.[5]

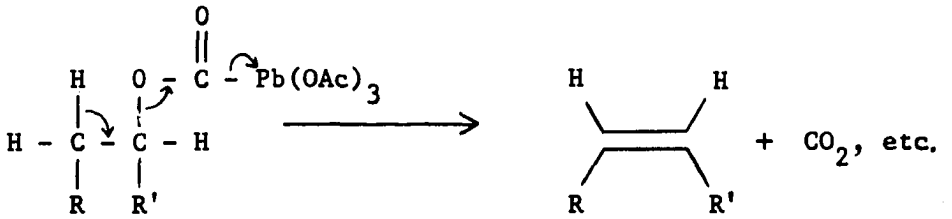
The use of lead tetraacetate in the decomposition of organic acids had been studied from a theoretical point of view[6,7] but had not been used synthetically until 1958 when Grob [8,9] introduced the use of lead tetraacetate as a reagent for the bis-decarboxylation of 1,2-dicarboxylic acids. One molar equivalent of lead tetraacetate and two molar equivalents of pyridine or triethylamine were added to a solution of the diacid in benzene or acetonitrile and the reaction mixture was then heated at 50° for three hours. The yield of the olefin was 50-70%. The mechanism proposed by Grob was transesterification of one of the two carboxyl groups by lead tetraacetate, followed by abstraction of the

other acid proton by the base and finally fragmentation. This new



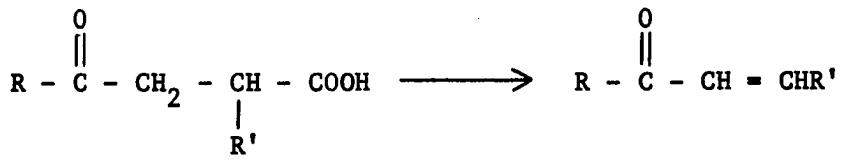
reaction offered the advantage that the yield of olefin was generally higher and more reproducible than with lead dioxide.[9]

Büchi[10] proposed a similar fragmentation mechanism for the reaction of a monocarboxylic acid with lead tetraacetate in the absence of any base.



Various free radical mechanisms[6,7,11] have been proposed for lead tetraacetate reactions but were discounted by Corey[12] who suggested that a free radical mechanism occurred only when no reasonably stable carbonium ion could be formed. Corey found that under the same reaction conditions used by Grob[9] both meso- and d,l-2,3-diphenylsuccinic acid gave trans-stilbene although cis-stilbene was found to be stable under the reaction conditions.

Prior to the present study, Kelly[13] had examined the reaction of lead tetraacetate with a number of γ-ketoacids of the following type:



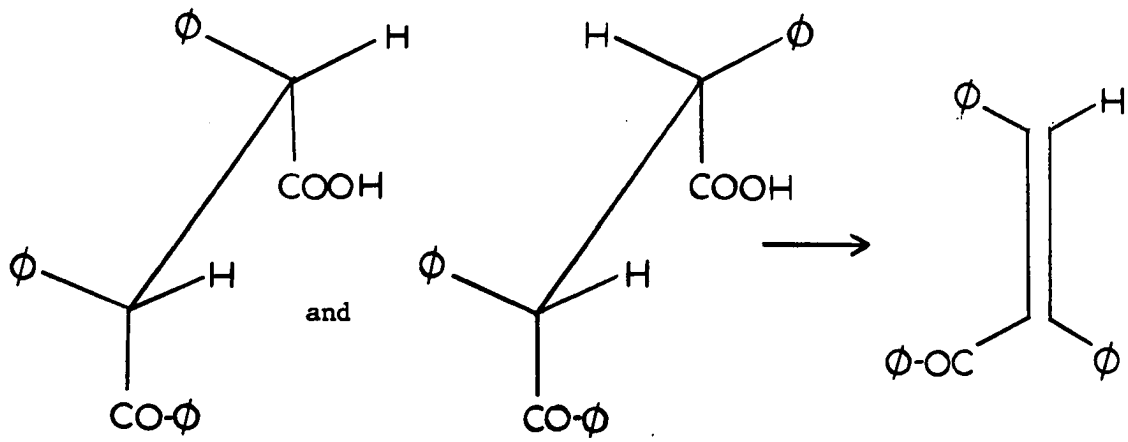
Acid	R	R'	Ketone
1	Me	Ø	5
2	Ø	Ø	6
3	Ø	H	7
4	Ø	Me	8

The reaction conditions used for the oxidative decarboxylation of these γ-ketoacids were similar to those of Büchi;[10] that is, no base, such as pyridine or triethylamine, was added as in Grob's[9] procedure. The γ-ketoacid was dissolved in benzene or toluene, the solution brought to reflux and solid lead tetraacetate was slowly added. The lead tetraacetate used in these experiments was a commercial product (Arapahoe Chemical Company) and was moist with acetic acid. By using a slight excess of the acid so that lead tetraacetate was the limiting reagent, the reaction could be followed by the starch-iodide test for an oxidizing agent, in this case lead (IV), and was worked up when lead (IV) was no longer present. No base was added and when pyridine was used as the solvent, the yields of α,β-unsaturated ketones were even lower than when benzene or toluene was the solvent.

α-Phenyl-β-acetylpropionic acid (1)[14] underwent oxidative decarboxylation resulting in benzalacetone (5) in 64% yield based on the starting acid. In the same manner, α-phenyl-β-benzoylpropionic

acid (2)[15,16] gave chalcone (6) in 65% yield. β-Benzoylpropionic acid (3) afforded the first case in which the product, acrylophenone (7), appeared to be unstable to the reaction conditions. All attempts to isolate the ketone failed. Finally, the phenylhydrazine adduct, 1,3-diphenylpyrazoline,[17] was isolated in 35% yield. No recognizable product was isolated from the reaction of lead tetraacetate with α-methyl-β-benzoylpropionic acid (4).[18] The expected product, crotonophenone (8),[19] when treated with lead tetraacetate, gave the same product mixture as did the parent acid as judged by its infrared spectrum.

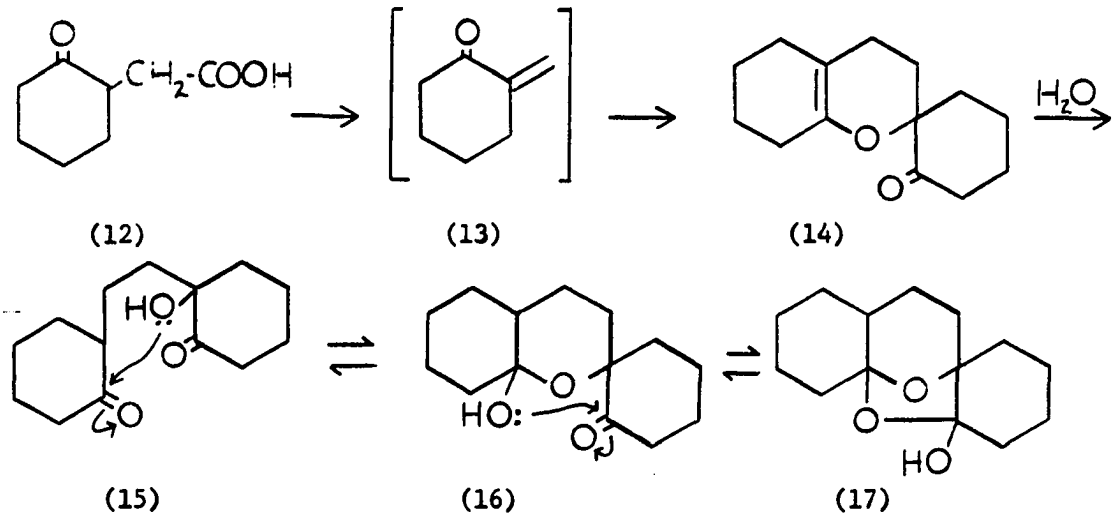
The stereochemistry of the lead tetraacetate reaction was elucidated by the following examples. Both erythro- and threo-α,β-diphenyl-β-benzoylpropionic acid[20] (9 and 10) were decarboxylated to the same mixture containing predominately trans-phenylchalcone (11).[21] Cis-phenylchalcone[22] did not rearrange to the trans isomer (11) under the reaction conditions.



(9) (10) (11)

RESULTS AND DISCUSSION

The purpose of this study was to extend the previous work to include cyclohexan-2-one acetic acid (12). α-Phenyl-β-benzoylpropionic acid (2) was decarboxylated in order to develop methods of analyzing the reaction products. The results were essentially the same as those of Kelly.[13] Although cyclohexan-2-one acetic acid, which was prepared by alkylation of the enamine of cyclohexanone with ethyl bromoacetate and then hydrolysis of the resulting ester,[23] consumed lead tetraacetate in the usual way, the expected produce, 2-methylenecyclohexanone (13), could not be isolated in the usual work up procedure. Instead, another product, (17), formed by a Diels-Alder reaction of the



(12) (13) (14)

(15) (16) (17)

expected 2-methylenecyclohexanone (13), followed by hydrolysis of the resulting vinyl ether and then hemiacetal formation in the hydroxydione, was isolated. The structures of (15-17) were elucidated recently by Bohme *et al*[24] who obtained them in another reaction which initially formed 2-methylenecyclohexanone. Although these three forms exist in equilibrium in solution, only (17) was isolated in this work since its high volatility caused it to sublime during attempted distillation. If (15) and (16) were present, they apparently were completely converted to the single isomer.

An examination of these results leads to the conclusion that the reaction shows promise of utility as a synthetic method for the more highly substituted or conjugated unsaturated ketones, but would be unsatisfactory for those bearing no substituents, or only one alkyl substituent, in the β-position. However, as a degradative method, the reaction has been effectively employed in simplification of the carbon skeleton of a γ-keto acid derived from a natural product, even in the relatively unfavorable instance of a single β-alkyl substituent.[26]

EXPERIMENTAL

Oxidative Decarboxylation of α-Phenyl-β-benzoylpropionic acid (2). A solution of α-phenyl-β-benzoylpropionic acid[15,16] (10.16 g, 40 mmoles) dissolved in 400 ml of toluene was brought to reflux and lead tetraacetate (18.27 g, 37.5 mmoles calculated as 90% pure) added cautiously. The starch-iodide test was initially purple due to the oxidation of iodide to iodine by lead (IV) but after 30 minutes had become yellow due to the formation of lead (II) iodide. The reaction mixture was then filtered to remove the lead (II) acetate, washed with water, sodium carbonate and then again with water. After drying over sodium sulfate, the solvent was removed on a rotary evaporator under vacuum leaving a yellow oil which was filtered through basic alumina (50 g) in benzene. Removal of the solvent left an oily yellow solid (5.88 g) which was dried overnight in a vacuum desiccator to give chalcone,[25] m.p. 51-54° (5.38 g, 65%). The IR spectrum showed bands at 1668 cm^{-1} (carbonyl) and 1610 cm^{-1} (double bond).

The sodium carbonate solution from above was acidified with dilute hydrochloric acid and then extracted with ether. After washing the organic layer with water and drying over sodium sulfate, the solvent was removed on a rotary evaporator under vacuum leaving the recovered acid (0.72 g, 7%).

Synthesis of Cyclohexan-2-one Acetic Acid (12). The synthetis was originally described by Mondon.[20] A solution of cyclohexanone (100 g, 1.02 moles) and pyrrolidine (160 g, 2.25 moles) dissolved in 300 ml of benzene was refluxed for eight hours over 2 g of Dowex 50. The water was collected in a modified Dean-Stark separator. The reaction mixture was filtered and the solvent and excess pyrrolidine were removed on a rotary evaporator under vacuum. The residue was distilled and the enamine was collected at 106-107°/10 mm (113 g, 73%). Considerable foaming was encountered during the distillation.

Ethyl bromoacetate (132 g, 0.70 moles) was added to a solution, heated to 50°, of the enamine (83 g, 0.55 moles) dissolved in 80 ml of methanol at such a rate (30 minutes required for addition) that methanol was continuously distilled from the reaction mixture. One hour after the addition had begun the remaining methanol was distilled using a steam bath. Water (100 ml) was added to the residue and the mixture was stirred for an additional hour at 70°. The heat was removed and the stirring was continued for one more hour. The reaction mixture was saturated with sodium chloride and extracted with ether. After drying over sodium sulfate, the solvent was removed on a rotary evaporator under vacuum and the residue was distilled. Ethyl cyclohexan-2-one acetate was collected at 129-130°/10 mm (55.3 g, 55%).

The ester was hydrolyzed by stirring overnight at room temperature with 125 ml of concentrated hydrochloric acid. The reaction mixture was placed in an ice bath and made basic with 70 g of sodium hydroxide dissolved in 150 ml of water. The aqueous solution was washed with ether and then acidified with dilute sulfuric acid. The acidic

solution was saturated with sodium chloride and extracted with ether. After drying over sodium sulfate, the solvent was removed on a rotary evaporator under vacuum and the residue was distilled. Cyclohexan-2-one acetic acid was collected at 163-164°/1.5 mm and crystallized in the receiver, m.p. 70.5-71.5°. The IR spectrum (KBr) showed a very broad band at 3450 cm^{-1} (hydroxyl) and a broad band at 1713 cm^{-1} (carbonyl). The NMR spectrum ($CDCl_3$) exhibited a signal at δ 10.89, s, 1H (acid proton) and a broad methylene envelope.

Oxidative Decarboxylation of Cyclohexan-2-one Acetic Acid. A solution of cyclohexan-2-one acetic acid (1.25 g, 8 mmoles) dissolved in 80 ml of benzene was brought to reflux and lead tetraacetate (3.66 g, 7.5 mmoles, calculated as 90% pure) was cautiously added. The starch-iodide test, as before, indicated the reaction was complete in three hours. The reaction mixture was filtered and the water soluble product removed by washing with three 100 ml portions of water. The combined aqueous solutions were saturated with ammonium sulfate, the precipitated lead sulfate removed by filtration, and then extracted with five 100 ml portions of ether. After drying over sodium sulfate, the solvent was removed on a rotary evaporator under vacuum leaving an oily residue (0.69 g). A distillation was attempted but when the pot was dry, virtually nothing (0.06 g) was found in the receiver. A white crystalline solid was found in the dry ice-acetone trap. Recrystallization from aqueous ethanol gave a white solid, m.p. 144-145° (0.52 g, 55%) identified[24] as (17). The IR spectrum (KBr) exhibited sharp band at 3430 cm^{-1} (hydroxyl) and a very characteristic fingerprint region. The

NMR spectrum ($CDCl_3$) showed a signal at δ 3.89, broad s, 1H (hydroxyl) and a broad methylene envelope.

SUMMARY

Several examples of oxidative decarboxylation of γ-ketoacids were discussed illustrating the method to be a mild, high yield means of decarboxylation and synthesis of α,β-unsaturated ketones in some cases. It would appear that ketones containing an exo-methylene or simple alkyl group cannot be synthesized but more highly substituted or conjugated ketones can be synthesized by this method.

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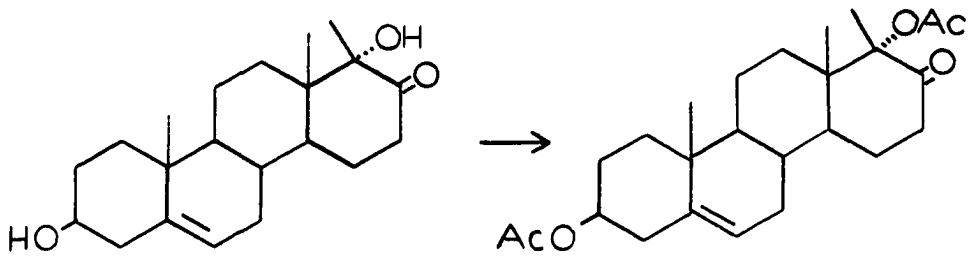
II. ACETYLATION OF TERTIARY ALCOHOLS

INTRODUCTION

The difficulty with which tertiary alcohols acetylate is well known. Several methods have been developed for this reaction. Boulez[1,2] used rather severe conditions of refluxing acetic anhydride and sodium acetate. Ketene and a trace of sulfuric acid[3,4] have been successfully tried but this requires a ketene generator. Ott[5] refluxed the alcohol, acetic anhydride and pyridine with good results. Mesnard and Bertucat[6,7] made a thorough study of the acetylation of alcohols by a reaction mixture of p-toluene sulfonic acid or phosphoric acid dissolved in acetic anhydride and dioxane. Under the conditions used, tertiary alcohols required 24 hours to acetylate. Acetic anhydride and perchloric acid[8,9] have also been used but the reaction is incomplete and produces substantial quantities of olefins.

Boron trifluoride etherate and acetic anhydride have recently[10,11] been proposed as a reagent for cleaving methyl ethers to a mixture of the corresponding acetate and olefin. An attempt to cleave the ether linkage of mammosin[12] led to almost quantitative acetylation of the tertiary alcohol. Another example of acetylation of a tertiary alcohol using boron trifluoride etherate has been reported.[13] When Δ^5 -3β,17a(α)-dioxy-D-homo-androsten-17-one (1) was treated with boron trifluoride

etherate, acetic acid and acetic anhydride, the diacetate (2) was formed in 37% yield.

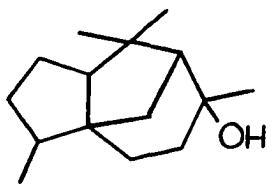


(1) (2)

These examples suggested promise and formed the basis for a further study of the acetylation of tertiary alcohols using boron tri-fluoride etherate and acetic anhydride.

RESULTS AND DISCUSSION

The acetylation of cedrol (3) with one molar equivalent of boron trifluoride etherate and three molar equivalents of acetic anhydride in



(3)

either ether or ethyl acetate for one hour at -10° led to a mixture of unreacted alcohol, both endo and exo olefins, and the desired acetate. The unreacted alcohol was only a minor component while the two olefins comprised 37% of the product mixture with the endo olefin (α-cedrene) predominating to the extent of 5:1. The yield of the desired product, the acetate, was 47%.

In most experiments with cedrol the analysis of the product mixture was accomplished by the use of NMR spectroscopy. The signal at approximately δ 1.3, due to the methyl carbinol, was unique to the alcohol. The IR spectrum of the product mixture was also used to determine the presence or absence of low concentrations of unreacted alcohol. The acetate had two characteristic signals at approximately δ 1.5 due to

the methyl under the acetate and δ 1.9 due to the methyl of the acetate moiety. The signals at δ 4.5 and 5.2 were used to characterize the exo and endo olefins respectively. Thus by using the ratio of the signal intensities at δ 1.3/1.5, the alcohol/acetate composition could be determined and the ratio of the intensities at δ 4.5/2x5.2 could be used to determine the exo/endo relationship.

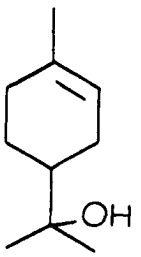
In an effort to increase the yield of acetate, the reaction conditions were varied. Since unreacted alcohol remained, an attempt to force the reaction to completion was made. When a ten-fold excess of acetic anhydride was added, there was no unreacted alcohol but only a small amount of acetate was formed. The product mixture contained predominately the endo olefin with a few percent of the exo olefin. In a similar manner, a ten-fold excess of boron trifluoride etherate again left no unreacted alcohol but in this case virtually no acetate was formed. The product was almost entirely the endo olefin with only a trace of exo olefin.

Virtually no reaction was observed when only a catalytic amount of boron trifluoride etherate was used, thus one molar equivalent was used as a minimum. The reaction was normally carried out at -10°. This would be close to the minimum temperature because when the reaction was attempted with the usual ratio of reagents but at -30°, the alcohol was unchanged. It was possible that deacetylation of the acetate rather than, or in conjunction with, dehydration of the alcohol or collapse of a common intermediate was the source of the olefins.[9] In order to check the possibility that the acetate was being formed rapidly and then undergoing deacetylation, the reaction time was decreased. This led to

incomplete conversion of the alcohol and olefin was still formed. This fact does not distinguish between the three possibilities mentioned above.

1-Methylcyclohexanol and t-butyl alcohol underwent partial acetylation and partial elimination in the same manner as did cedrol but in both examples, the olefins were stripped from the solution before the products were analyzed. Thus, in both cases, the product of the reaction was the corresponding acetate, in yields similar to the cedrol case, contaminated with the starting alcohol.

α-Terpineol (4) introduced a new problem. When α-terpineol was



(4)

acetylated with three molar equivalents of acetic anhydride, in addition to the usual product mixture of alcohol, acetate and olefins, a second acetate was formed as evidenced by a second signal at δ 1.90 in the NMR spectrum. The analysis of the product mixture in the case of α-terpineol was accomplished, as in the case of cedrol, by the use of the NMR spectrum. The signal at δ 1.1, due to the methyl carbinol, was unique to the alcohol while the acetate showed signals at δ 1.4, due to the methyl under the acetate, and δ 1.85, assigned to the methyl of the acetate

moiety. The unidentified acetate group, possibly arising from addition of acetic acid to the double bond, gave rise to a signal at δ 1.90. The olefin region of the spectra was not as useful as it was in the cedrol spectra since α-terpineol contains a double bond but traces of the exo olefin could be distinguished by the signal at δ 4.5

When only a 20% excess of acetic anhydride instead of the usual three molar equivalents was added, no second acetate was formed but the reaction was only two-thirds complete. When a 75% excess of acetic anhydride was added, the reaction went more towards completion but the second acetylated compound was also formed.

EXPERIMENTAL

Acetylation of Cedrol. To a solution, cooled to -10°, of cedrol (1.1010 g, 5.0 mmoles) dissolved in 25 ml of ether, were successively added 1.50 ml of acetic anhydride (15.9 mmoles) and 0.70 ml of boron trifluoride etherate (5.5 mmoles) both precooled to -10°. The reaction mixture was allowed to stand at -10° for one hour. The mixture was diluted with 100 ml of ether and the solution was washed with 10% pyridine, 10% hydrochloric acid, 10% sodium bicarbonate and distilled water. After drying over sodium sulfate, the solvent was removed on a rotary evaporator under vacuum. The crude produce (1.2113 g) was a pale yellow oil. The IR spectrum (film) exhibited weak bands at 3420 cm^{-1} (hydroxyl), 1645 cm^{-1} (double bond) and 835 cm^{-1} (trisubstituted double bond) and a strong band at 1732 cm^{-1} (acetate). The NMR spectrum (neat) showed signals at δ 1.83, s, (acetate methyl); 4.55, m, (terminal methylene) and 5.23, m, (vinyl hydrogen).

The crude product was chromatographed on 50 g of Florisil. Fractions 6-8 (hexane) contained a hydrocarbon tentatively identified as α-cedrene (0.310 g, 31%). The IR spectrum (film) exhibited bands at 1655, 810 and 796 cm^{-1} (trisubstituted double bond). The NMR spectrum (CCl_4) contained signals at δ 0.84, d, J = 6.5 cps, 3H (secondary methyl); 0.94, s, 3H (quaternary methyl); 1.02, s, 3H (quaternary methyl); 1.66, m, 3H (vinyl methyl) and 5.20, m, 1H (vinyl hydrogen). Fractions 10-24

(hexane) contained a hydrocarbon tentatively identified as β-cedrene (0.062 g, 6%). The IR spectrum (film) exhibited bands at 1642 and 880 cm^{-1} (terminal methylene). Fractions 26-31 (ether) contained cedryl acetate (0.6036 g, 47%). The IR spectrum (film) exhibited a strong band at 1731 cm^{-1} (acetate carbonyl). The NMR spectrum (CCl_4) showed signals at δ 0.84, d, J = 5 cps, 3H (secondary methyl); 0.97, s, 3H (quaternary methyl); 1.20, s, 3H (quaternary methyl); 1.50, s, 3H (methyl under acetate) and 1.85, s, 3H (acetate methyl).

Acetylation of Cedrol (Large Excess of Acetic Anhydride). To a solution cooled to -10° of cedrol (1.1137 g, 5.0 mmoles) dissolved in 25 ml of ethyl acetate, were successively added 4.80 ml of acetic anhydride (50.8 mmoles) and 0.75 ml of boron trifluoride etherate (5.9 mmoles) each precooled to 0°. The reaction mixture was allowed to stand at -10° for one hour and then worked up as before. The crude product (1.2431 g) was a pale yellow oil. The IR spectrum (film) exhibited a weak band at 1732 cm^{-1} (acetate) and significant bands at 1655, 811 and 797 cm^{-1} (trisubstituted double bond). The NMR spectrum (CCl_4) showed signals at δ 0.84, d, J = 6.5 cps, 3H (secondary methyl); 0.95, s, 3H (quaternary methyl); 1.02, s, 3H (quaternary methyl); 1.67, m, 3H (vinyl methyl), 5.20, m, 1H (vinyl hydrogen) due to the endo olefin; very weak signals at 1.50, s, (methyl under acetate); 1.83, s, (acetate methyl); due to the acetate and 4.52, m (terminal methylene); due to the exo olefin indicating the sample was predominantly the endo olefin with traces of acetate and exo olefin.

Acetylation of Cedrol (Large Excess of Boron Trifluoride Etherate). To a solution cooled to -10° of cedrol (1.1188 g, 5.0 mmoles) dissolved in 25 ml of ethyl acetate, were successively added 0.75 ml of acetic anhydride (7.9 mmoles) and 6.30 ml of boron trifluoride etherate (49.9 mmoles) each precooled to 0°. The reaction mixture was allowed to stand for one hour at -10° and worked up as before. The crude product (1.0142 g) was a colorless oil. The IR spectrum (film) exhibited a very weak band at 1732 cm^{-1} (acetate) and significant bands at 1655, 811, and 797 cm^{-1} (trisubstituted double bond). The NMR spectrum (CCl_4) exhibited signals at δ 0.84, d, J = 6.5 cps, 3H (secondary methyl); 0.95, s, 3H (quaternary methyl); 1.02, s, 3H (quaternary methyl); 1.67, m, 3H (vinyl methyl) and 5.20, m, 1H (vinyl hydrogen) due to the endo olefin, α-cedrene, and a very weak signal at 4.52, m, (terminal methylene) due to the exo olefin. The ratio of endo/exo olefin was 15:1.

Acetylation of Cedrol (Catalytic Amount of Boron Trifluoride Etherate). To a solution cooled to -10° of cedrol (1.1189 g, 5.0 mmoles) dissolved in 25 ml of ethyl acetate, were successively added 0.75 ml of acetic anhydride (7.9 mmoles) and 0.10 ml of boron trifluoride etherate (0.8 mmoles) each precooled to 0°. The reaction mixture was allowed to stand at -10° for one hour and then worked up as before. The crude product (1.1211 g) was a white solid. The IR spectrum (KBr) exhibited a strong band at 3325 cm^{-1} (hydroxyl). The NMR spectrum (CCl_4) showed signals at δ 0.83, d, J = 6 cps, 3H (secondary methyl); 0.95, s, 3H (quaternary methyl); 1.21, s, 3H (quaternary methyl); 1.27, s, 3H

(methyl under hydroxyl) and 2.20, s, 1H (hydroxyl). Both the IR and NMR spectra were identical to the spectra of the starting cedrol.

Acetylation of Cedrol (Low Temperature). To a solution cooled to -30° in a dry ice-tetralin bath, of cedrol (1.1149 g, 5.0 mmoles) dissolved in 25 ml of ethyl acetate, were successively added 0.75 ml of acetic anhydride (7.9 mmoles) and 0.75 ml of boron trifluoride etherate (5.9 mmoles) each precooled to 0°. The reaction mixture was allowed to stand at -30° for one hour and then worked up as before. The crude product (1.1152 g) was a white solid. The NMR spectrum (CCl_4) was virtually identical with that of cedrol (as above) except for a very weak signal at δ 1.88, s, (acetate methyl).

Acetylation of Cedrol (Short Reaction Time). To a solution cooled to -10° of cedrol (1.1118 g, 5.0 mmoles) dissolved in 25 ml of ethyl acetate, were successively added 0.75 ml of acetic anhydride (7.9 mmoles) and 0.70 ml of boron trifluoride etherate (5.5 mmoles) each precooled to 0°. The reaction mixture was allowed to stand for only five minutes and then worked up as before. The crude product was a milky liquid (1.2596 g). The IR spectrum (film) exhibited significant bands at 3490 cm^{-1} (hydroxyl) and 1732 cm^{-1} (acetate). The NMR spectrum (CCl_4) contained the signals previously assigned to the alcohol, acetate and both olefins. The ratio of the intensities of the signals at δ 1.27 (methyl under alcohol) and 1.50 (methyl under acetate) was 1/2 indicating that the reaction had proceeded to at least 2/3 completion.

Acetylation of 1-Methylcyclohexanol. To a solution, cooled to -10°, of 1-methylcyclohexanol (0.5774 g, 5.1 mmoles) dissolved in 25 ml of ethyl acetate, were successively added 0.75 ml of acetic anhydride (7.9 mmoles) and 0.75 ml of boron trifluoride etherate (5.9 mmoles) each precooled to 0°. The reaction mixture was allowed to stand for one hour at -10° and worked up as before. The crude product was a slightly yellow liquid (0.5751 g, 73%). The IR spectrum (film) exhibited a very weak band at 3445 cm^{-1} (hydroxyl) and a strong band at 1731 cm^{-1} (acetate). The NMR spectrum (neat) showed signals at δ 1.34, s, 3H (methyl under acetate) and 1.81, s, 3H (acetate methyl). The olefins formed in the reaction had been removed with the solvent and the product mixture was primarily (90%) the acetate.

Acetylation of t-Butyl Alcohol. To a solution, cooled to -10°, of t-butyl alcohol (5.8263 g, 78.6 mmoles) dissolved in 250 ml of ether, were successively added 23 ml of acetic anhydride (244 mmoles) and 5 ml of boron trifluoride etherate (32.6 mmoles) each precooled to 0°. The reaction mixture was allowed to stand at -10° for one hour. The reaction mixture was worked up as before except that after drying over sodium sulfate instead of removing the solvent on a rotary evaporator, the entire sample was distilled through an 18" Nester/Faust spinning band column rated at 23 theoretical plates. After the solvent was removed the following fractions were collected:

Fraction 1 (b.p. 70-93°) 0.6751 g

The IR spectrum (film) exhibited strong bands at 3450 cm^{-1} (hydroxyl) and 1739 cm^{-1} (acetate).

Fraction 2 (b.p. 93-93.5°) 2.8189 g

The IR spectrum (film) exhibited a significant band at 1739 cm^{-1} (acetate). The NMR spectrum (neat) contained signals at δ 1.42, s, 9H (t-butyl group under acetate) and δ 1.88, s, 3H (acetate methyl).

Fraction 3 (b.p. 93.5-94°) 0.8304 g

The IR and NMR spectra were identical with those of Fraction 2.

The yield of t-butyl acetate (b.p. 93-94°) was 3.6493 g (40%).

Acetylation of α-Terpineol. To a solution, cooled to -10°, of α-terpineol (1.5278 g, 9.9 mmoles) dissolved in 25 ml of ether, were successively added 3 ml of acetic anhydride (31.7 mmoles) and 1 ml of boron trifluoride etherate (8 mmoles) each precooled to 0°. The reaction mixture was allowed to stand at -10° for one hour and then worked up in the normal manner. The crude product was a pale yellow oil. The IR spectrum (film) exhibited weak bands at 3490 cm^{-1} (hydroxyl) and 883 cm^{-1} (terminal methylene) and strong bands at 1732 cm^{-1} (acetate) and 814 and 795 cm^{-1} (trisubstituted double bond). The NMR spectrum (neat) showed strong signals at δ 1.39, s, (geminal methyls under acetate); 1.62, broad s, (vinyl methyls); 1.86, s, (acetate methyl) and 5.34, m, (vinyl hydrogen) and very weak signals at 1.09, s, (geminal methyls under alcohol); 2.46, s, (hydroxyl) and 4.64, m, (terminal methylene). In addition there was a moderately strong signal at δ 1.90, s, apparently due to a second acetate moiety. The ratio of the intensities of the signals at δ 1.09 (alcohol) / 1.39 (acetate) was 1/19. The ratio of the signals at δ 1.90 (unidentified acetate) / 1.86 (terpinyl acetate) was 2/5.

Acetylation of α-Terpineol (20% Excess of Acetic Anhydride). To a solution, cooled to -10°, of α-terpineol (1.4348 g, 9.1 mmoles) dissolved in 25 ml of ether, were successively added 1 ml of acetic anhydride (11.0 mmoles) and 1 ml of boron trifluoride etherate (8.0 mmoles) each precooled to 0°. The reaction mixture was allowed to stand at -10° for 18 hours and worked up as usual. The crude product was a pale yellow oil (1.6992 g). The NMR spectrum (neat) exhibited signals at δ 1.09, s, (geminal methyls under alcohol); 1.39, s, (geminal methyls under acetate); 1.62, broad s, (vinyl methyls); 1.86, s, (acetate methyl); 2.49, s, (hydroxyl) and 5.34, m, (vinyl hydrogen). The signal at δ 1.90 was absent and the ratio of the intensities of the signals at δ 1.09 (alcohol) / 1.39 (acetate) was 1/2 indicating the reaction was more than 2/3 complete before the second acetate formed.

Acetylation of α-Terpineol (75% Excess of Acetic Anhydride). To a solution, cooled to -10°, of α-terpineol (1.4104 g, 9.1 mmoles) dissolved in 25 ml of ether, were successively added 1.5 ml of acetic anhydride (15.8 mmoles) and 1 ml of boron trifluoride etherate (8 mmoles) each precooled to 0°. The reaction mixture was allowed to stand for one hour and then worked up as before. The crude product was a pale yellow oil (1.6520 g). The NMR spectrum (neat) was similar to the previous spectrum except that the signal at δ 1.90 due to the unidentified acetate was present. The ratio of the intensities of the signals at δ 1.09 (alcohol) / 1.39 (acetate) was 1/5 and the ratio of the signals at δ 1.90 (unidentified acetate) / 1.86 (terpinyl acetate) was 2/5.

SUMMARY

Although boron trifluoride etherate and acetic anhydride quantitatively acetylated mammosin,[12] the reaction is not a general one for tertiary alcohols. The yield of acetate is approximately 40-50% which is in the area of many of the other methods cited[4,8,9] but not as high a yield as others.[2,5,7] The reagent offers the advantages of relatively mild reaction conditions, short reaction time, and simple reaction equipment.

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III. SESQUITERPENOIDS ISOLATED FROM OCTOCORALLIA

INTRODUCTION

The occurrence of sesquiterpenoid hydrocarbons in a number of marine invertebrates, known as gorgonians or octocorals, has been noted previously,[1,2] although isolation of pure compounds and their identification was not undertaken. In the present work, these hydrocarbon fractions were examined in more detail with the objective of developing methods of separation to obtain pure compounds and to establish their identity. The hydrocarbon fractions of the volatiles of two species, Eunicea mammosa and Pseudoplexaura porosa, have been examined and the structures of one hydrocarbon from each have been elucidated. A third species, Pseudopterogorgia americana, afforded four hydrocarbons whose structures were examined.

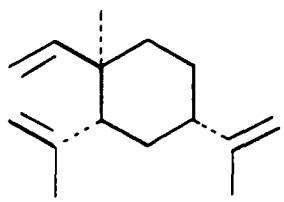
While in the process of examining the steam volatile components of Gorgonia ventalina, several chromatographic fractions were tested for activity against tubercule bacilli since the extract of this species had shown activity previously.[3] The fraction eluted immediately after the hydrocarbons showed activity. There were two compounds in this fraction which were not present in either the preceding or following fractions, both of which showed no activity. The major component was isolated and elemental analysis and spectral data showed it to be a

sesquiterpenoid benzofuran. The NMR spectrum narrowed the possible structures to two isomers and the structure was established by synthesis of both.

RESULTS AND DISCUSSION

A. Sesquiterpene Hydrocarbon from Eunicea mammosa

The sesquiterpene hydrocarbon content of Eunicea mammosa (0.1% of dry weight) was isolated by chromatography (Florisil) of the volatile components of the pentane extract and purified by preparative gas chromatography (SE-30) to separate a small amount (less than 1%) of a second hydrocarbon. Elemental analysis and molecular weight determination (204, m.s.) indicated the composition $C_{15}H_{24}$, and the excellent correspondence between its physical properties (n_D^{25} 1.4910, d_4^{25} 0.8825, $[\alpha]_D^{25}$ + 15.1°) and IR spectrum (Fig. 1) with published data[4,5] established the identity of the hydrocarbon as (+)-β-elemene (1).



(1)

The NMR (Fig. 2) and mass (Fig. 3) spectra were in accord with the structure assigned to (-)-β-elemene by Sorm, et al.[6] who synthesized the hydrocarbon from (-)-elemol. The correlation of (-)-elemol with

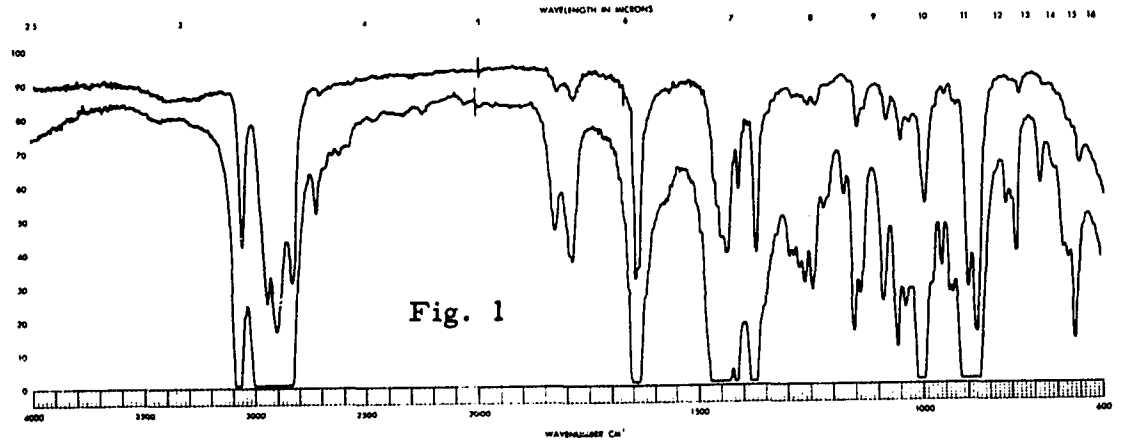


Fig. 1

β-Elemene

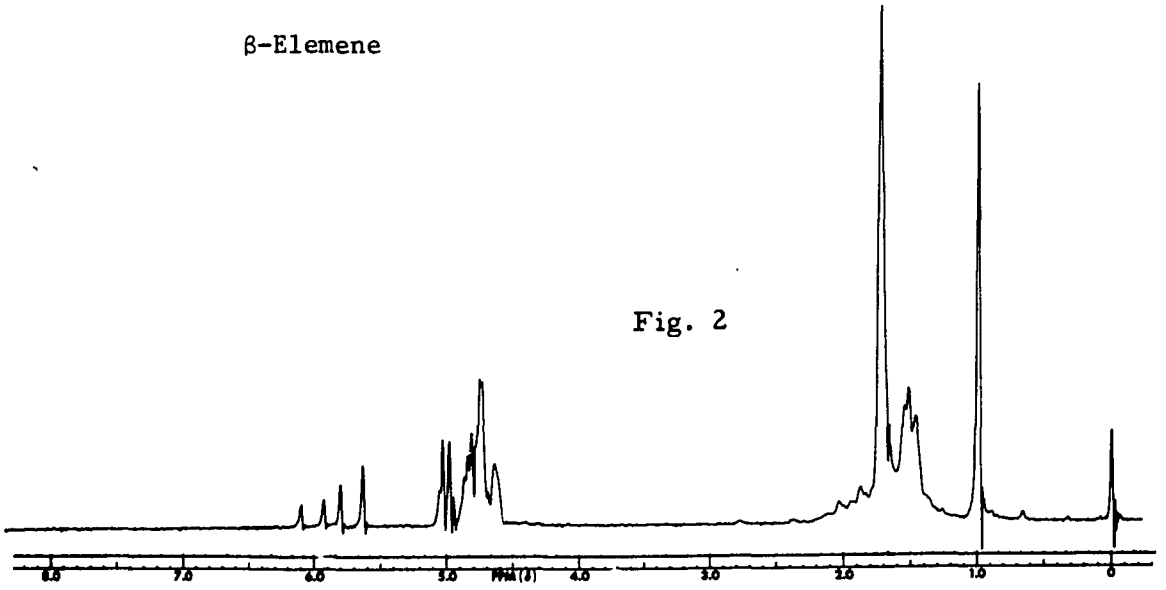


Fig. 2

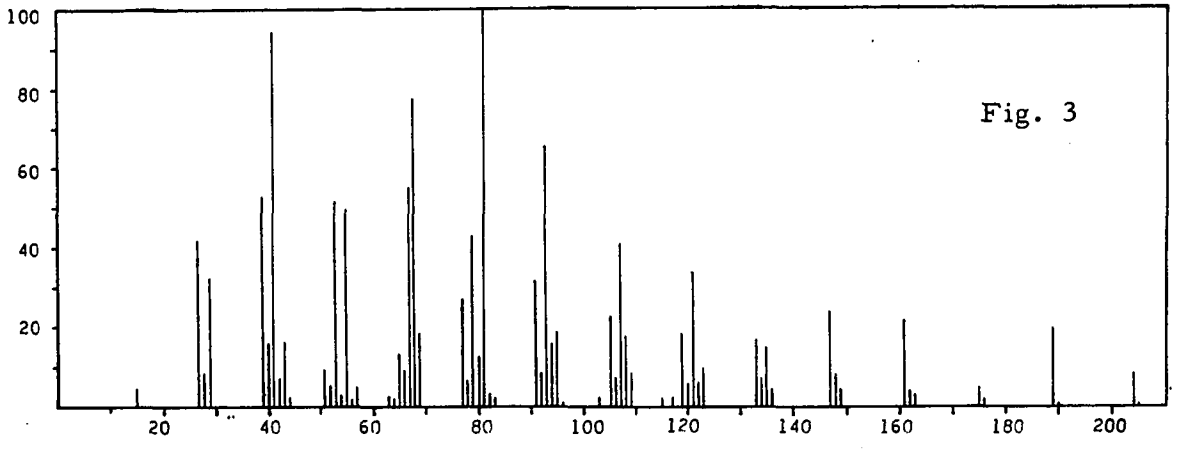
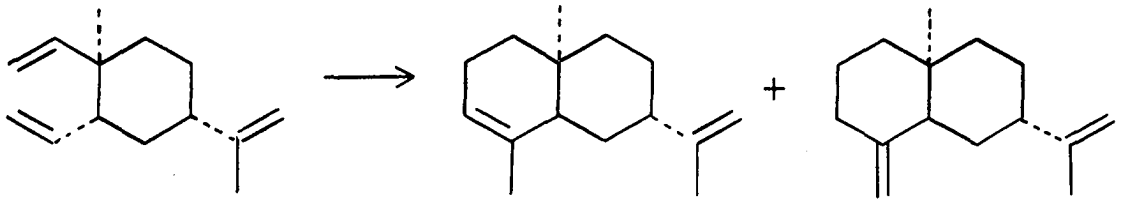


Fig. 3

saussurea lactone of known absolute configuration[7] established the absolute configuration of (+)-β-elemene to be that depicted in (1).

In addition to singlets at δ 0.98 (3H) and δ 1.71 (6H) due to the bridgehead and vinyl methyl groups respectively, the NMR spectrum (neat liquid) displayed signals due to a total of seven vinyl protons. The lone non-terminal vinyl proton appearing as a quartet (1H) centered at δ 5.87, with apparent coupling constants, J_{AB} and J_{BC}, of 10 and 18 cps, was shown (NMDR) to be coupled with the proton appearing as a quartet (1H) at δ 5.02 and with the unresolved multiplet centered at δ 4.86 which is responsible for the fine detail on the downfield side of the broad band at δ 4.58-4.92 due to the remaining terminal vinyl protons. The three coupled protons constitute the ABC system anticipated for the vinyl residue.

When Eunicea mammosa was chromatographed in hexane on silicic acid in an attempt to isolate β-elemene by a means other than preparative gas chromatography, extensive ring closure occurred, due to the not unexpected acid lability of β-elemene, resulting in a mixture of (+)-α



(1) (2) (3)

and (-)-β-selinene (2 and 3). This mixture of α- and β-selinenes was never completely separated. Preparative gas chromatography yielded two samples that were of sufficient purity to establish the identities of

the hydrocarbons by IR and NMR characterizations and on the basis of physical constants.[8,9]

An earlier suggestion[1] that the hydrocarbons, as well as other terpenoids found in gorgonians, originate at least in part with the unicellular algae (zooxanthellae) hosted by the invertebrates, has now been confirmed for the elemene. Intact zooxanthellae, isolated by blendor maceration and sedimentation of fresh animal, provided a small amount of extract whose hydrocarbon fraction contained two major components by gas chromatography (SE-30), one of which was shown to have the same retention time as (+)-β-elemene isolated from the gross animal/plant colony. The NMR and IR spectra of the total hydrocarbon fraction isolated from the zooxanthellae included all signals found in the spectra of (+)-β-elemene. The second hydrocarbon deteriorated rapidly when exposed to the air and could not be isolated. This deterioration is the most likely explanation of the fact that the second hydrocarbon was not encountered in the isolation of elemene from the dried animal/plant colony. Another possible explanation might be local or seasonal variations in the chemical composition of the colony.

Although the (-) form of β-elemene is widely distributed in terrestrial plants, the (+) form has only been encountered twice.[10,11] It is interesting to note that one[10] of these two sources is also marine, specifically, a Japanese brown alga.

B. Sesquiterpene Hydrocarbon from Pseudoplexaura porosa

The sesquiterpene hydrocarbon fraction of Pseudoplexaura porosa (0.5% of dry weight) was isolated by chromatography (Alumina) of the volatile components of the hexane extract. The yield of hydrocarbon was higher than obtained from the whole colony since only the tips of the plant/animal colony were extracted. Gas chromatography (LAC-1-R-296) indicated there were three major components, A-10%, B-50%, and C-35%. Only component C could be obtained pure by fractional distillation through a spinning band column. Elemental analysis and molecular weight determination (204, m.s.) indicated the composition $C_{15}H_{24}$ and the excellent correspondence of its IR (Fig. 4) and mass (Fig. 6) spectra and index of refraction n_D^{25} 1.4983 with published data[12] established the identity of the hydrocarbon as (+)-β-ylangene.

The NMR spectrum (Fig. 5) was consistent with the structure assigned to β-ylangene by Hunter[12] who showed that β-ylangene could be isomerized to the well characterized α-ylangene.[13,14] The configuration of (+)-β-ylangene, isolated from Pseudoplexaura porosa, was not determined since the original work on the structure of β-ylangene[12] was carried out on such a small sample that the optical rotation of neither the β-ylangene nor the isomerization product, α-ylangene, was determined. Although the stereochemical relationship of α-ylangene to α-copaene of known absolute configuration[15-18] has been demonstrated,[14] only the relative configuration and not the absolute configuration is known. Thus the structure of the β-ylangene isolated from Pseudoplexaura porosa

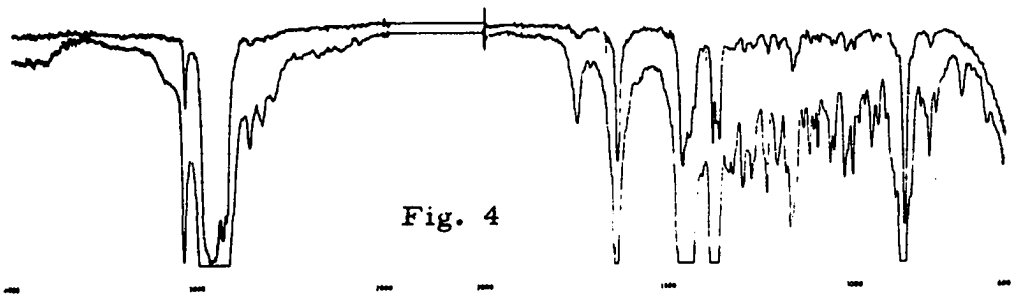


Fig. 4

β-Ylangene

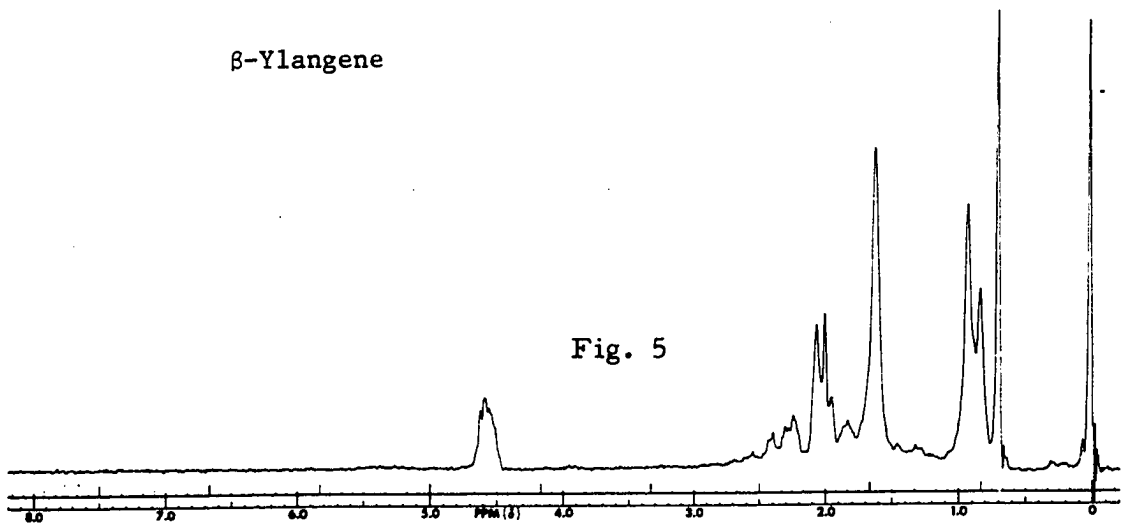


Fig. 5

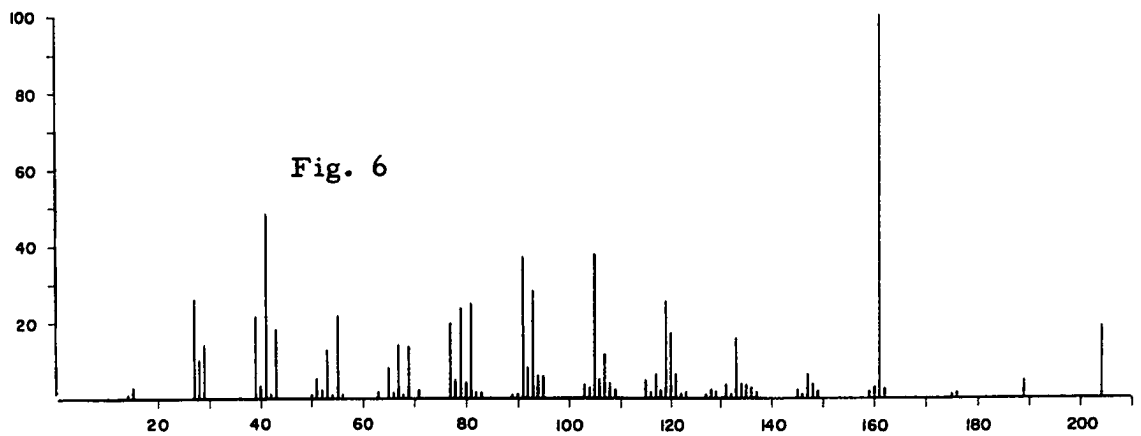
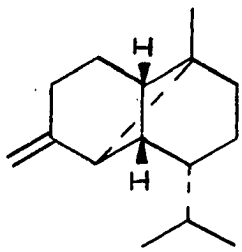


Fig. 6

would be as is shown in (4) or the enantiomer. Further work is now in progress on β-ylangene.[19]



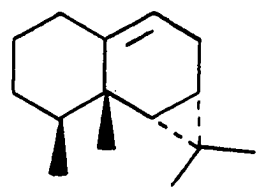
(4)

The NMR spectrum (neat) showed a methyl singlet at δ 0.68 (3H) due to the angular methyl on the cyclobutane ring. The diamagnetic shift exhibited by this signal was apparently due to the influence of the anisotropic π-electron cloud of the olefin function since the signal exhibited by the methyl in α-ylangene was normal, δ 0.80.[14] The isopropyl methyls appeared as a doublet at δ 0.85, J = 5.5 cps (6H) and the terminal methylene as a narrow multiplet at δ 4.58 (2H).

Some information about components A and B could be gleaned from the IR and NMR spectra of an impure sample which contained a mixture of the two in ratio of 1:5. The NMR spectrum showed that component A had at least one trisubstituted double bond (a weak signal at δ 5.19) whereas component B had no trisubstituted double bonds but instead contained a terminal methylene (signals at δ 4.52 and 4.71, approximately 1H each). This double bond must be unusual since in the IR spectrum, the band attributed to the terminal methylene occurred at 862 cm^{-1} instead of the normal 880-900 cm^{-1}.[20]

C. Sesquiterpene Hydrocarbons from Pseudopterogorgia americana

The sesquiterpene hydrocarbon fraction of Pseudopterogorgia americana (0.9% of dry weight) was isolated by molecular distillation of the hexane fraction from a chromatography (silicic acid) of the nonsaponifiable portion of the hexane and ether extracts. Chromatography on silver nitrate impregnated silicic acid[21] afforded samples of the four major hydrocarbons. No suitable elemental analysis could be obtained for the first hydrocarbon (7.6% of the total sesquiterpene fraction) due to the ease with which it underwent air oxidation. Molecular weight determination (204, m.s.) indicated a composition of $C_{15}H_{24}$ and the excellent correspondence of its physical properties (n_D^{25} 1.4975, d_4^{25} 0.9249, $[\alpha]_D^{25}$ + 80.9), IR spectrum (Fig. 7) and NMR spectrum (Fig. 8) with published data[22,23] established the identity of this hydrocarbon as (+)-9-aristolene (5). The absolute configuration, as shown in (5), had already



(5)

been established[22] by the fact that the air oxidation product, (+)-aristolone, was identical, except for the rotation, with a sample of (-)-aristolone of known absolute configuration.

The NMR and mass spectra (Fig. 9) were in agreement with the structure (5) proposed for (-)-9-aristolene by Sorm, et al.[24,25] The vinyl hydrogen appeared as a broad multiplet centered at δ 5.07. The

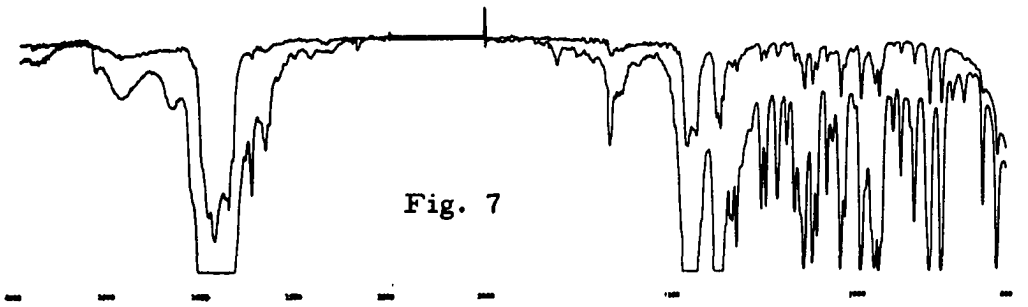


Fig. 7

(+)-9-Aristolene

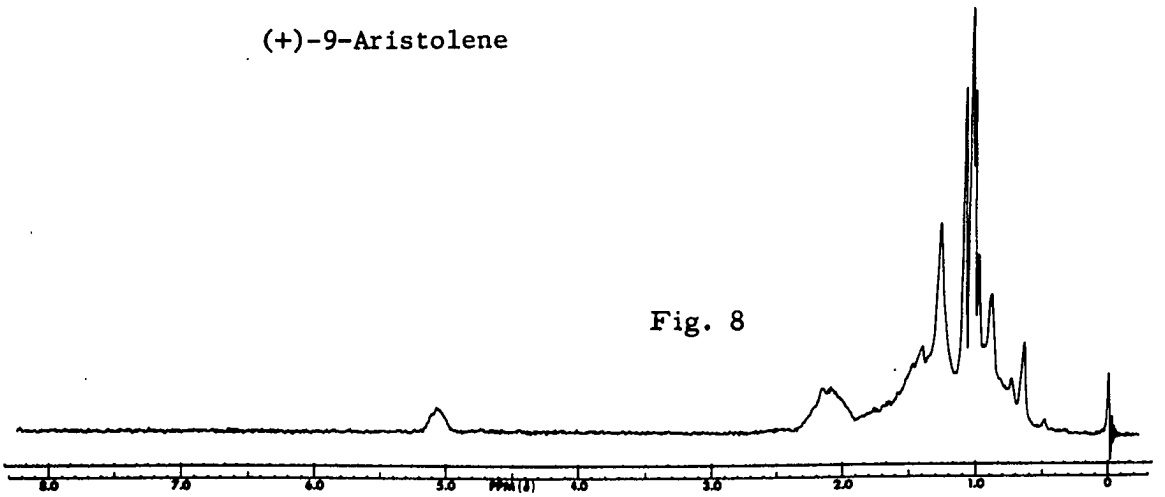


Fig. 8

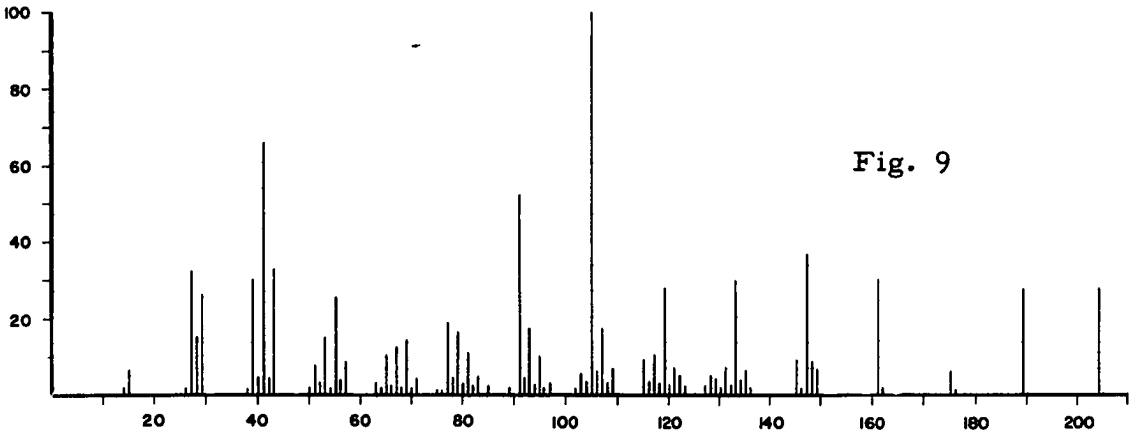
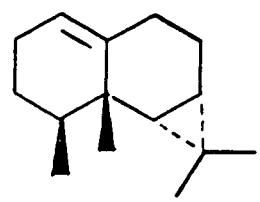


Fig. 9

allylic hydrogens, C-1 and C-8, also a broad multiplet, appeared at δ 2.12. In addition to the quaternary methyls appearing as singlets at δ 1.09, 1.04 and 1.02, the NMR spectrum showed a doublet at δ 0.94, J = 6 cps, due to the secondary methyl. The two cyclopropane hydrogens exhibited a complex multiplet centered at δ 0.65. It is unfortunate that the (+) isomer of 9-aristolene was given an entirely different name, α-ferulene, when it was first isolated by Carboni, et al.[22]

Elemental analysis and molecular weight determination (204, m.s.) of the second hydrocarbon (24.9% of the total) eluted from the column indicated a composition of $C_{15}H_{24}$. The excellent correspondence of its physical properties n_D^{25} 1.5005, d_4^{25} 0.9198, $[\alpha]_D^{25}$ - 78.5°), IR spectrum (Fig. 10) and NMR spectrum (Fig. 11) with published data[24,26] established the identity of this hydrocarbon as (-)-1(10)-aristolene (6).



(6)

The NMR and mass (Fig. 12) spectra are consistent with the structure proposed by Büchi[23] for (+)-1(10)-aristolene of known absolute configuration. In addition to singlets at δ 1.04, 1.00 and 0.96 due to the quaternary methyl groups the NMR spectrum showed a signal at δ 5.22 (1H) appearing as a double doublet due to the lone vinyl hydrogen. The

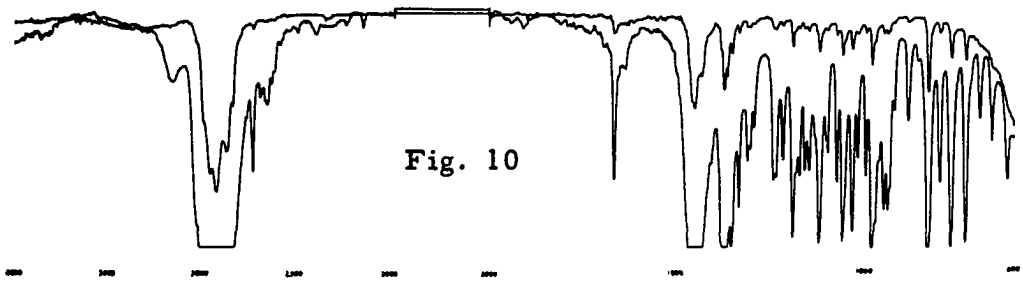


Fig. 10

(-)-1(10)-Aristolene

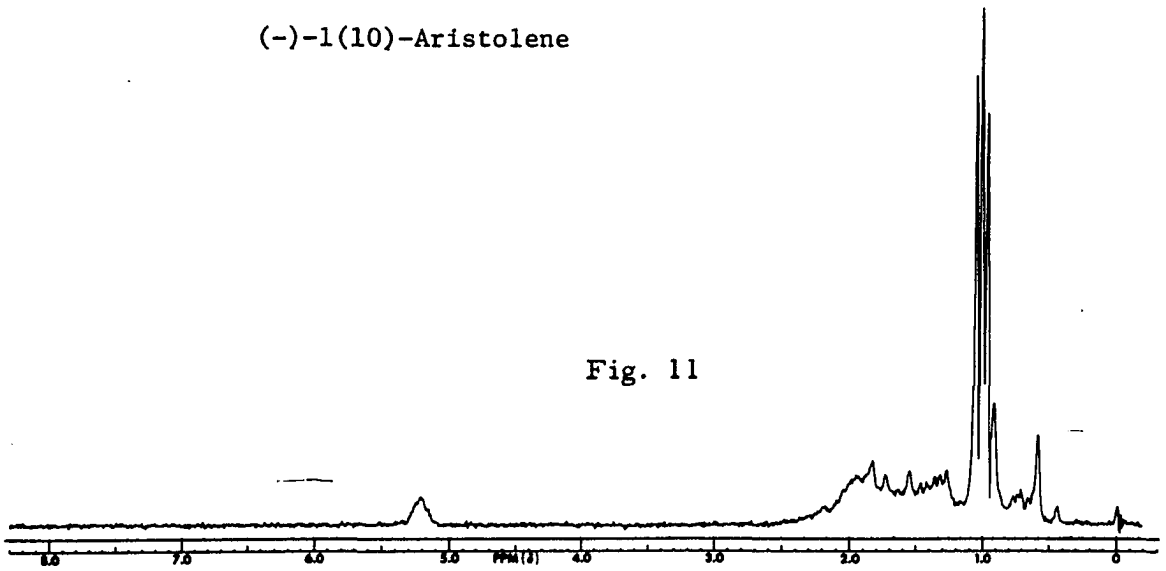


Fig. 11

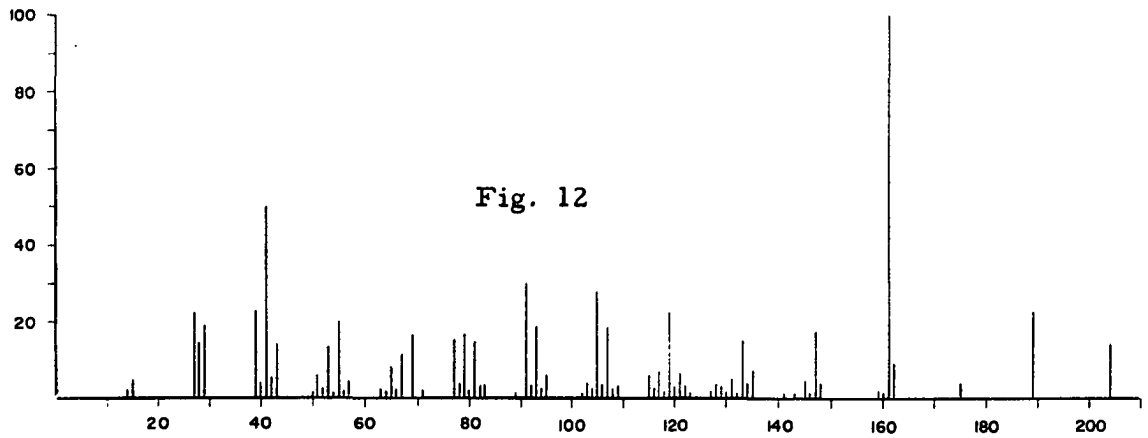
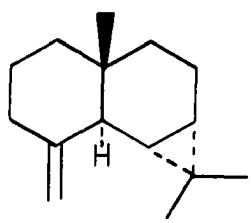


Fig. 12

secondary methyl gave rise to a doublet at δ 0.96, J = 7 cps. One leg of the doublet is superimposed on the singlet at δ 1.00. The cyclopropane hydrogens appeared as a multiplet centered at δ 0.59.

Previously (+)-1(10)-aristolene was known as both calarene and β-gurjunene. Calarene was shown not to be a single entity but a mixture of (+)-1(10)- and (-)-9-aristolenes[24,25] and thus the name was dropped. The name β-gurjunene was relinquished in favor of (+)-1(10)-aristolene since the carbon skeleton was already known as aristolane.[24]

The third hydrocarbon (8.5% of total) isolated from Pseudopterogorgia americana had a composition of $C_{15}H_{24}$ as indicated by elemental analysis and molecular weight determination (204, m.s.). The correspondence of its index of refraction (n_D^{25} 1.4992) and IR spectrum (Fig. 13) with published data[27] indicated the hydrocarbon was (+)-γ-maaliene (7).



(7)

The NMR (Fig. 14) and mass (Fig. 15) spectra were consistent with the structure assigned to γ-maaliene synthesized by Büchi[28] from (+)-γ maaliol of known absolute configuration. The terminal methylene hydrogens appeared as a multiplet centered at δ 4.79 and the geminal methyl groups displayed signals at δ 1.02 and 0.90. A singlet at δ 0.73 was assigned

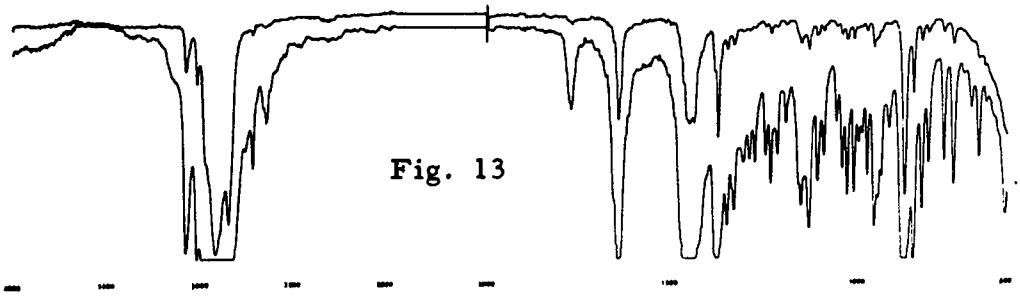


Fig. 13

γ-Maaliene

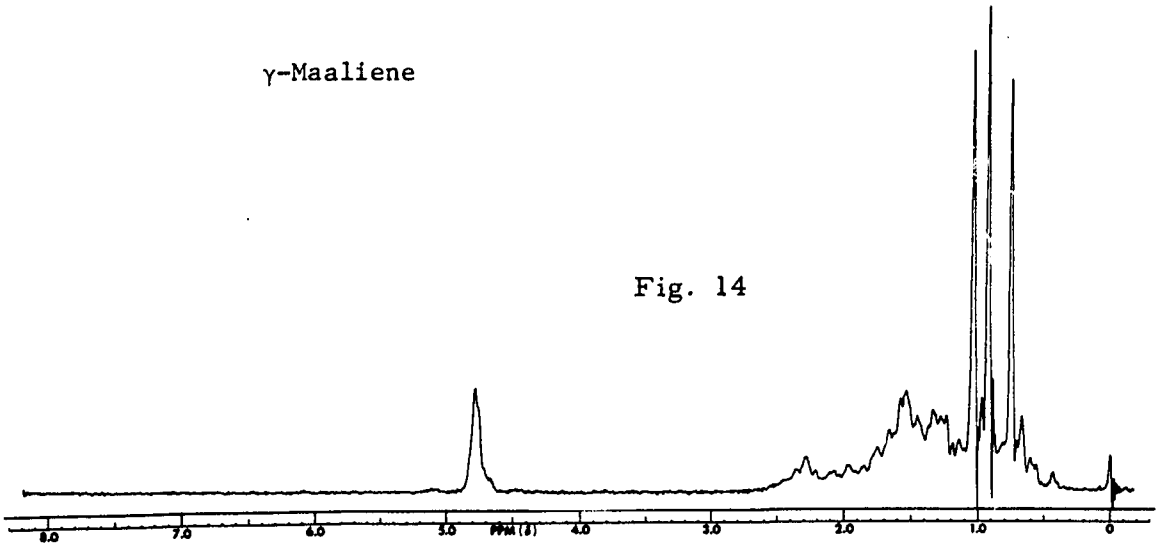


Fig. 14

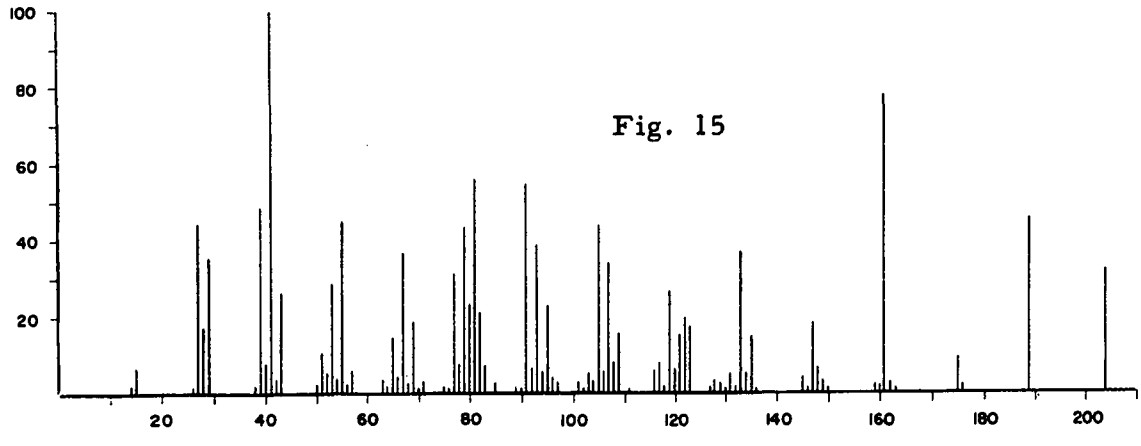


Fig. 15

to the angular methyl since a Dreiding model of γ-maaliene indicated this was the methyl group that would show a diamagnetic shift due to the anisotropy of the π electrons of the double bond. The cyclopropane hydrogens appeared as a multiplet centered at δ 0.67.

In order to determine the absolute configuration of (+)-γ-maaliene, the olefin was converted to the diol, m.p. 141-142°, $[\alpha]_D^{25}$-24.8 (c, 6.3 chloroform) with osmium tetroxide, and compared with a sample of (+)-γ-maalidiol of known absolute configuration kindly supplied by Dr. Büchi. The diols were identical in all respects except that the rotations were of opposite sign. Thus, the stereochemistry of (+)-γ-maaliene is that shown in (7). The d,l-γ-maalidiol was prepared by dissolving equal weights of the individual diols and then removing the solvent. The dl compound melted at 126-128°.

Although the thin layer chromatogram of (+)-γ-maaliene indicated it was a pure compound, it was later shown to contain 10% impurity by gas chromatography (LAC-1-R-296).[29] Thus, the physical properties and spectra recorded here will be subject to a slight modification in the future.

Elemental analysis and molecular weight determination (204, m.s.) indicated a composition of $C_{15}H_{24}$ for the fourth hydrocarbon (51.4% of the total). Its physical properties, n_D^{25} 1.5010, d_4^{25} 0.9108, $[\alpha]_D^{25}$ + 13.9) and spectra (Figs. 16-18) did not correspond to any known structure and so the hydrocarbon was called (+)-β-gorgonene (8).

The NMR spectrum (Fig. 17) showed in addition to a singlet at δ 0.79 due to a quaternary methyl, a doublet, J = 1.0 cps, at δ 1.55

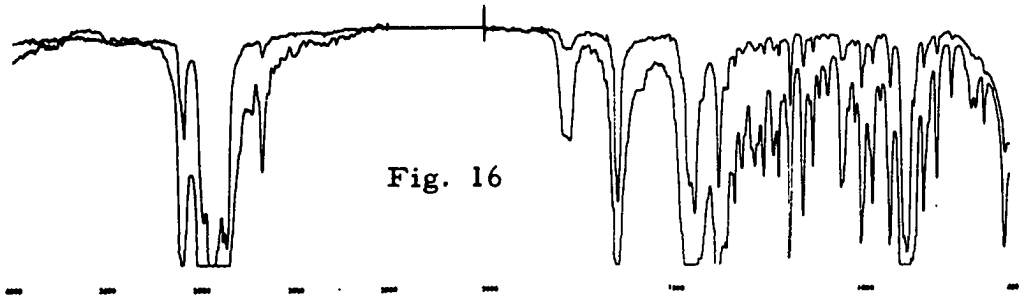


Fig. 16

β-Gorgonene

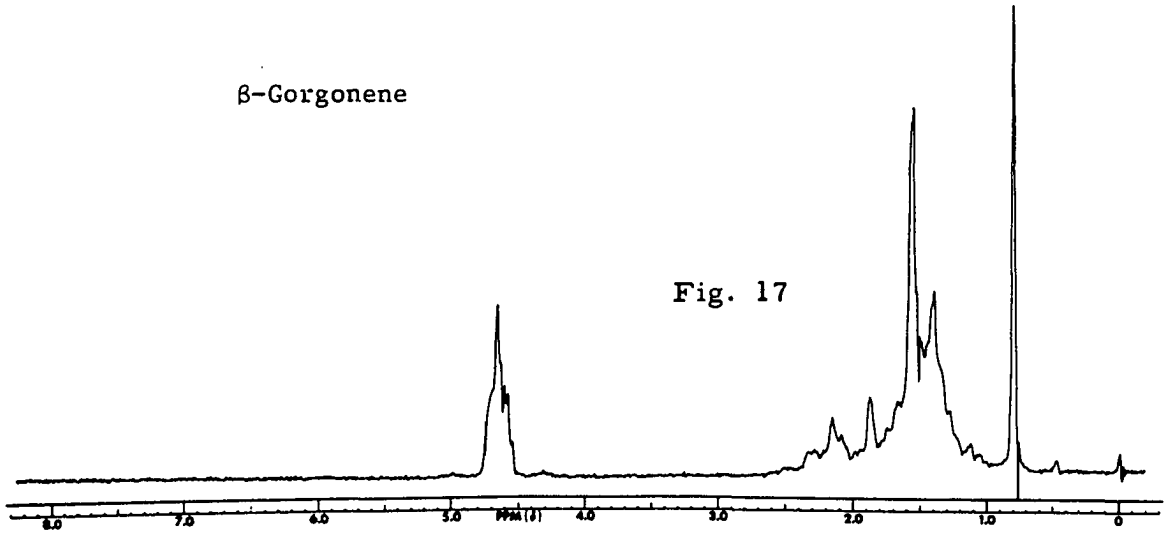


Fig. 17

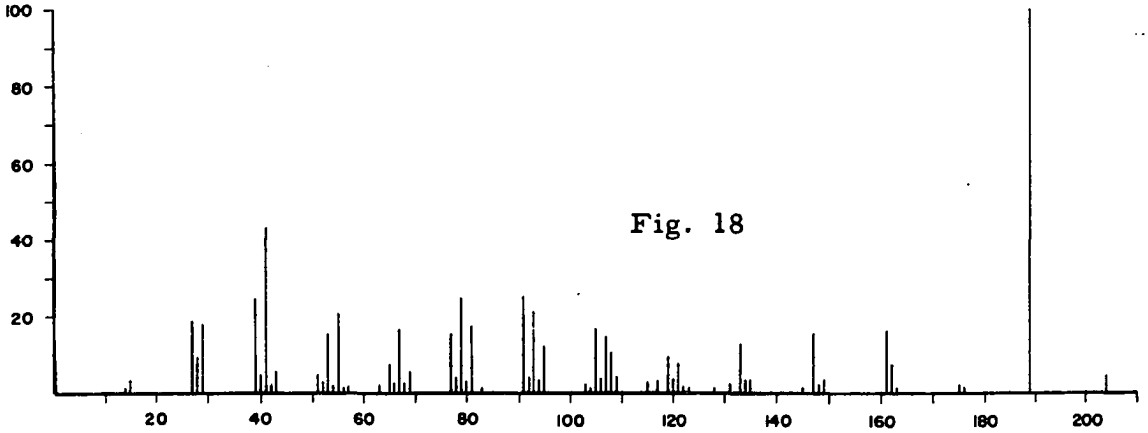
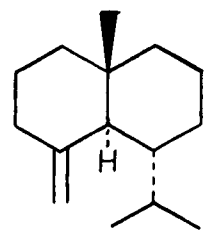


Fig. 18

due to a vinyl methyl and a complex multiplet at δ 4.66 due to four terminal methylene hydrogens. The most likely assignment of these data would be a bridgehead methyl, one terminal methylene and an isopropenyl group. These three structural features still leave many possible structures. The carbon skeleton could not be readily determined due to the extreme resistance to dehydrogenation. The olefin was unchanged even after heating with selinium at 340° for 20 hours or with palladium-charcoal at 250° for 24 hours.

β-Gorgonene was eluted from the silver nitrate-silicic acid column as a mixture of the hydrocarbon and a solid silver nitrate-olefin complex. The complex was filtered, recrystallized, m.p. 132.5-133.5, and the structure of the complex and thus of the olefin was determined using x-ray crystallography by D. van der Helm and M. B. Hossain.[30]



(8)

It is interesting to note that in the two cases in which a direct comparison can be made, (+)-9-aristolene and (-)-1(10)-aristolene, the enantiomer isolated from the marine source is the optical antipode of the more common form found in terrestrial sources. Both enantiomers have been isolated in the case of 9-aristolene but the (+) form has been isolated only once.[22] No direct comparison can be made in the case of

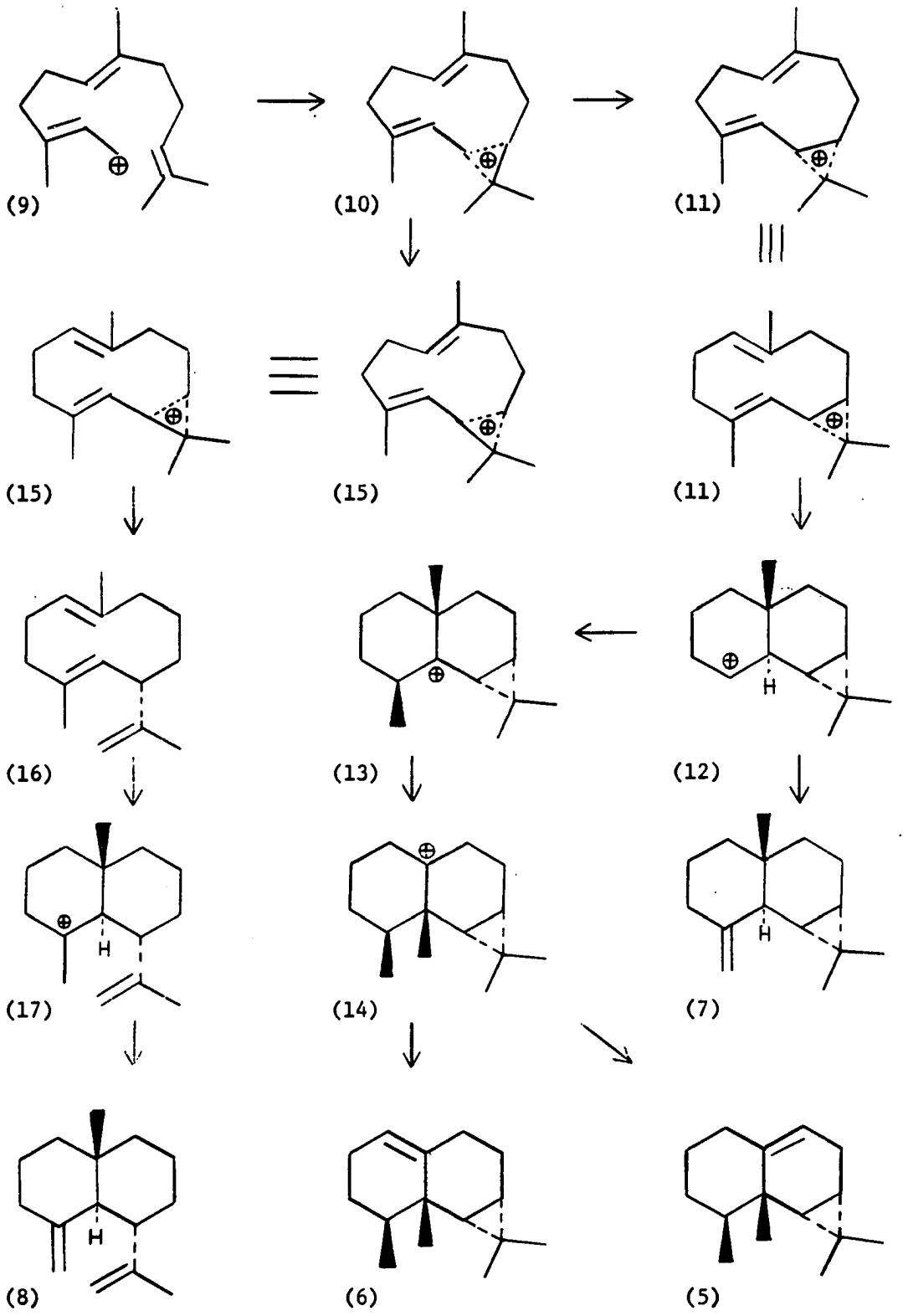
(+)-γ-maaliene since the olefin has not been found previously as a naturally occurring compound. However, (+)-γ-maaliene is the enantiomer of the γ-maaliene formed by dehydration of the common (+)-maaliol as was shown by a comparison of the diols.

A biosynthetic pathway can be proposed for the four olefins found in Pseudopterogorgia americana by making a slight modification of the proposal by Ourisson[26] of cyclization of the trans farnesyl cation (9) to the non-classical carbonium ion (10) which can lose a proton to form the ten-membered cyclic olefin (11). Closure of the large carbocyclic ring of (11) would lead to a carbonium ion (12) which could either lose a proton to give (+)-γ-maaliene (7) or rearrange to the carbonium ion (13) by a 1,2-hydride shift. Migration of the angular methyl in (13) would lead to the carbonium ion (14) which could lose a proton to give either (+)-9-aristolene (5) or (-)-1(10)-aristolene (6).

A 1,2-hydride shift in the non-classical carbonium ion (10) would lead to another non-classical carbonium ion (15) and loss of a proton from this structure would give the ten-membered cyclic olefin (16). Closure of the large carbocyclic ring would lead to the carbonium ion (17) and loss of a proton would give (+)-β-gorgonene (8).

D. Sesquiterpenoid Hydrocarbon from Gorgonia ventalina

Air dried Gorgonia ventalina was extracted with pentane and after removal of the solvent, the extract was steam distilled. The yellow distillate was crudely separated into nine fractions by chromatography (Florisil). The various fractions were tested in vitro for activity against


(9)
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(17)
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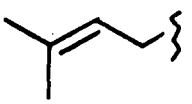
(8)
(6)
(5)

tuberculosis and histoplasmosis. None of the fractions showed activity against histoplasmosis but one fraction showed activity against tuberculosis at a dosage level of 1000 μg/ml. The major component of this fraction was isolated by chromatography (silicic acid and silver nitrate impregnated silicic acid). Elemental analysis and molecular weight determination, 214 (m.s.) indicated a composition of $C_{15}H_{18}O$. The IR spectrum (Fig. 19) indicated an aromatic compound, showed no hydroxyl or carbonyl absorption, but did exhibit a band characteristic of an ether. The UV spectrum was consistent with a benzofuran,[31] λ_{max} 249 mμ (ε = 16,000), 281 mμ (ε = 4,200) and 287 mμ (ε = 6,200).

The NMR spectrum (Fig. 20) displayed two signals which appeared as broad singlets at δ 1.50 (3H) and δ 1.64 (3H) due to two vinyl methyl groups. On an expanded scale (sweep width 100 cps), the signals appeared as poorly resolved doublets J = 0.7 and 1.0 cps respectively. The NMR spectrum also showed a multiplet at δ 2.30 (2H) due to an allylic methylene and a triplet with additional fine splitting at δ 5.19 (1H) due to a vinyl hydrogen. The vinyl hydrogen was shown (NMDR) to be coupled to both the allylic methylene (the finely split vinyl proton triplet collapsed to a narrow multiplet) and to the vinyl methyls (the finely split triplet collapsed to a triplet not further split and the methyl doublets collapsed to two singlets). These facts would lead to the following partial structure (18):



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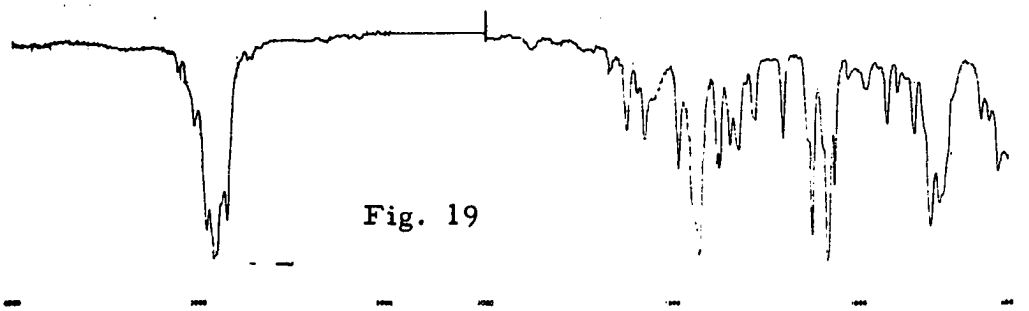


Fig. 19

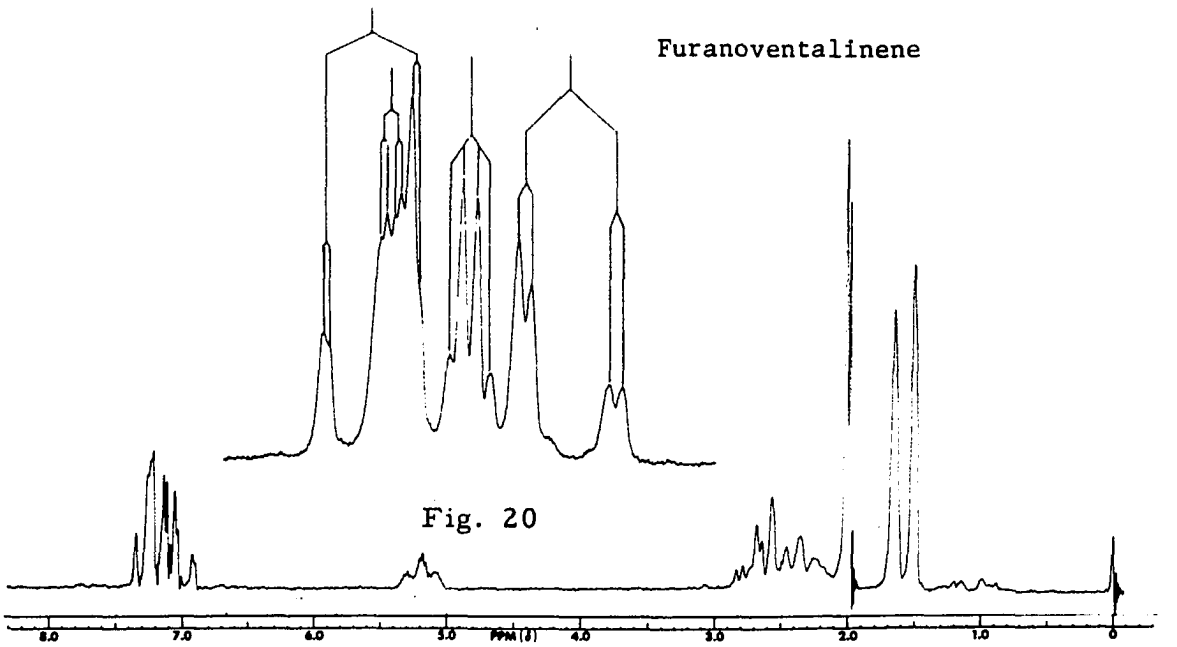


Fig. 20

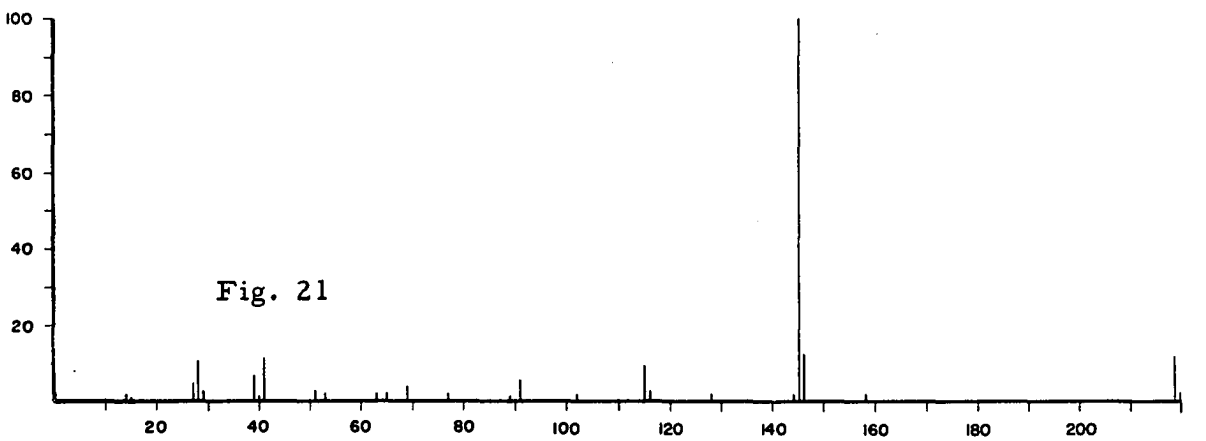
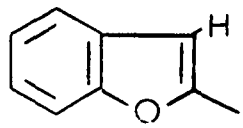


Fig. 21

The most characteristic signal in the NMR spectrum was the doublet at δ 1.97, J = 1.1 cps (3H), which was shown (NMDR) to be coupled (each collapsed to a singlet) with the quartet at δ 7.13 (1H). The magnitude of the J value, 1.1 cps, was characteristic of allylic coupling and the methyl group and proton were assigned a vicinal relationship on the furan ring. There are two possibilities for these assignments--either a methyl at C-2 and a proton at C-3 (19) or a methyl at C-3 and a proton at C-2 (20). The signals were assigned as in (20) since the



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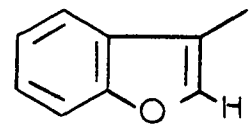


(20)

chemical shift of the furan hydrogen, δ 7.13, corresponded more closely to the α-hydrogen of benzofuran itself which has been shown to be in the aromatic region, δ 7.27, than to the β-hydrogen which was located upfield at δ 6.41.[32]

Including the three aromatic protons this accounts for all but one methylene group which was assigned as a benzylic methylene through which the side chain (18) was attached to the aromatic nucleus (20). The benzylic methylene appeared as one-half of an A_2B_2 system[33] centered at δ 2.51 (2H). The other half of the A_2B_2 system, the allylic methylene, did not appear as the usual A_2B_2 pattern since the splitting was further complicated by coupling with the vinyl proton. The benzylic methylene could be more readily distinguished in the NMR spectrum of the tetrahydro

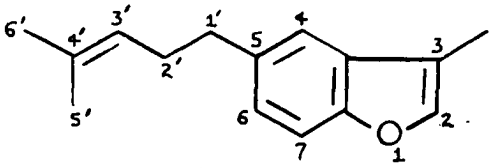
derivative [shown as two partial structures (21)]. In addition to a multiplet at δ 6.75 (3H) due to the aromatic protons, the NMR spectrum

(21)

of the tetrahydro compound displayed double doublets at δ 4.61, J = 8.5 and 7.5 cps (1H), and δ 4.00, J = 7.5 and 7.0 cps (1H) due to the two protons α to the ether on C-2. The multiplicity observed was interpreted as being due to mutual coupling of the two protons of the C-2 methylene in addition to coupling of the individual protons with the proton on C-3 which appeared as a very broad multiplet centered at δ 3.44, J = 8.5, 7.0 and 6.5 cps. The benzylic methylene appeared as a triplet at δ 2.51, J = 7.0 cps. The signal was no longer complicated, an A_2B_2 as before, since hydrogenation had converted the allylic methylene to a normal aliphatic methylene and shifted its signal further upfield away from the signal due to the benzylic methylene. The two doublets at δ 1.29, J = 6.5 cps (3H) and δ 0.88, J = 6.0 cps (6H) were assigned to the C-3 methyl and the isopropyl groups respectively.

The question remaining was the position of attachment of the side chain (18) to the aromatic nucleus (20). A close examination of the aromatic region of the NMR spectrum of the parent benzofuran (inset Fig. 21) revealed that in addition to the furan proton, there were signals present for three distinct aromatic protons with ortho, meta, and

<u>para</u> coupling. The fact that all three types of aromatic coupling were present indicated a 1,2,4-substituted aromatic system. This still left two possible structures which were called furanoventalinene A (22) and B (23).



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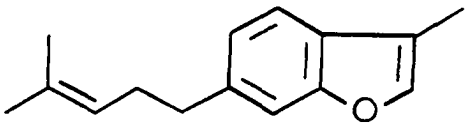


(23)

Both structures are consistent with the predominate cleavage pattern observed in the mass spectrum (Fig. 21). Other than the parent ion peak, the only other peak that was over 10% of the total ionization occurred at m/e 145. This was interpreted as resulting from cleavage of the bond between the benzylic and allylic carbons (C-1' and C-2'). Both structures are also in accord with the fact established by Elvidge and Foster[32] that in the NMR spectra (neat) of various methylbenzofurans, the aromatic protons on C-5 and C-6 were found upfield from the C-2 proton and the C-4 and C-7 protons were found downfield.

Black and Heffernan[34] observed a solvent dependence of the chemical shifts and J values of the NMR absorptions of the benzenoid protons of benzofuran itself. Furanoventalinene was studied in other solvents with the intent of establishing the position of the side chain based upon a correlation of the chemical shifts and J values with those of Black and Heffernan. Table 1 compares the values of Black and

Heffernan with the values assigned on the basis of structure (22) and those based on structure (23). The last column compares the values of Black and Heffernan taken in acetone with values of the present example taken in acetonitrile. The solvent dependence of the chemical shift in

TABLE 1

Solvent Dependence of Chemical Shifts and J Values*

Proton	Structure (22)			Benzofuran			Structure (23)		
	Neat	CCl_4	CH_3CN	Neat	CCl_4	C_3H_6O	Neat	CCl_4	CH_3CN
C-4	7.25	7.20	7.32	7.41	7.49	7.64	7.29	7.32	7.44
C-5	--**	--	--	7.10	7.14	7.23	6.98	6.97	7.07
C-6	6.98	6.97	7.07	7.11	7.20	7.30	--	--	--
C-7	7.29	7.32	7.44	7.45	7.42	7.52	7.25	7.20	7.27
$J_{4,5}$	--	--	--	8.0	7.8	7.8	8.0	8.0	8.1
$J_{4,6}$	1.2	1.4	1.4	1.0	1.2	1.3	--	--	--
$J_{4,7}$	0.6	0.5	0.7	0.7	0.8	0.7	0.6	0.5	0.7
$J_{5,7}$	--	--	--	1.2	0.9	0.9	1.2	1.4	1.4
$J_{6,7}$	8.0	8.0	8.1	8.0	8.0	8.3	--	--	--

*Chemical shifts are given in δ, p.p.m. from TMS and J values are given in c.p.s.

**Indicates there would be no value for that proton in that structure.

the case of furanoventalinen B (23) is more like that of benzofuran than is the dependence of furanoventalinene A (22). In particular both the

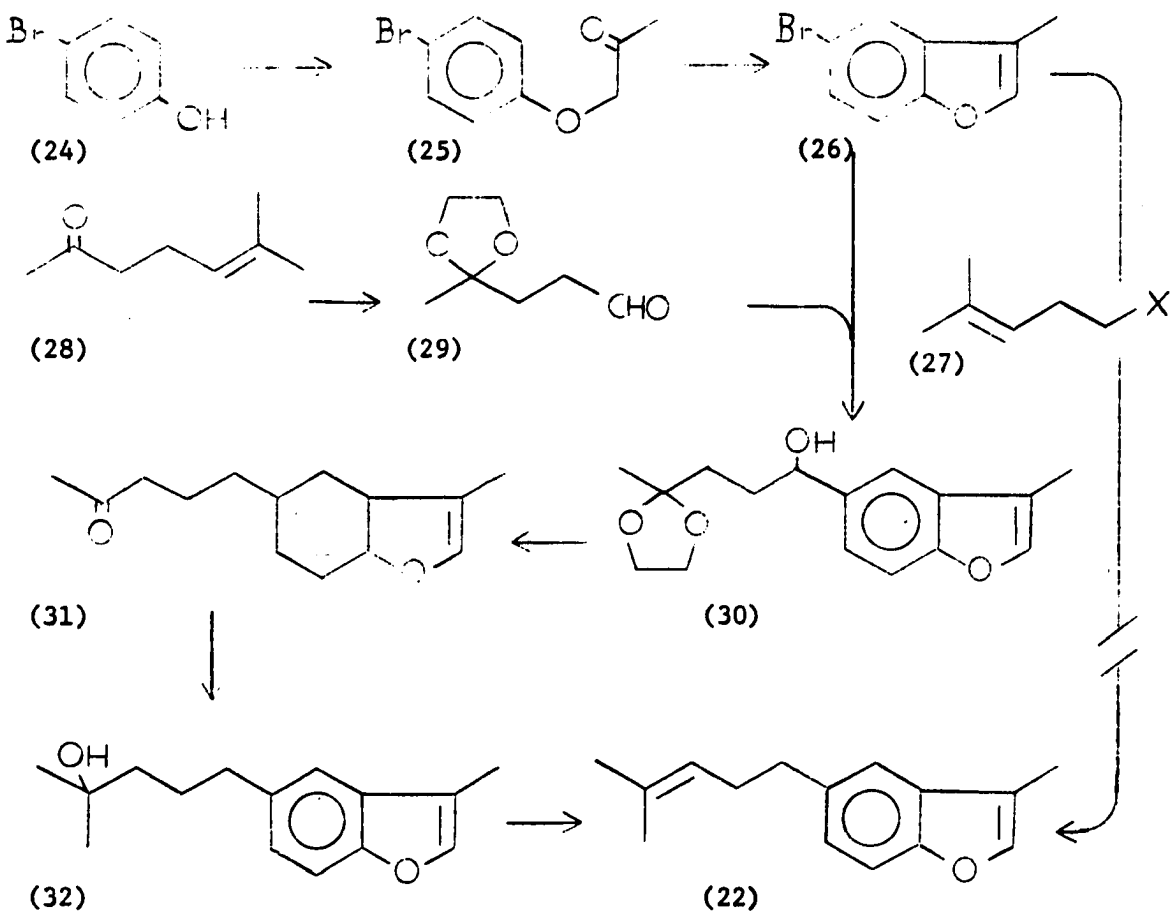
upfield shift of the C-7 proton in carbon tetrachloride and the downfield shift of the C-4 proton in carbon tetrachloride observed for benzofuran is followed by furanoventalinene B (23) and not by furanoventalinene A (22). On the other hand the solvent dependence of the J values in the case of furanoventalinene A (22) follow the pattern of benzofuran more closely than do the values of furanoventalinene B (23). In particular, the meta J value in the case of structure (22), $J_{4,6}$, increases when the spectrum is run in carbon tetrachloride solution as compared to the spectrum of the neat liquid as does the $J_{4,6}$ value of benzofuran. However, the meta J value in the case of structure (23), $J_{5,7}$, increases in carbon tetrachloride while that J value, $J_{5,7}$, decreases in the case of benzofuran.

Since the attempt to determine the position of the side chain from the NMR spectra led to ambiguous results, both possibilities still remained. The question was settled by synthesis of both isomers. The easier of the two possibilities, 3-methyl-5-(4'-methyl-3'-pentenyl) benzofuran (22) was synthesized first. O-Alkylation of p-bromophenol (24) with chloroacetone[35] gave p-bromophenoxyacetone (25) which underwent cyclodehydration to 3-methyl-5-bromobenzofuran (26) with polyphosphoric acid. Two well established methods of accomplishing the cyclodehydration of a phenoxyketone to a benzofuran, cold concentrated sulfuric acid[36] and refluxing phosphorus oxychloride,[37] were tried but met with no success in this particular example.

At this point several types of coupling reactions were attempted between the aryl bromide (26) and the desired side chain in

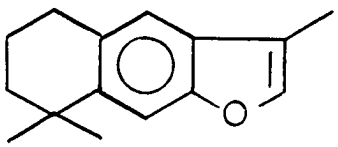
the form of its bromide or tosylate (27). Among the methods attempted are the following: coupling of the aryl Grignard reagent and the alkyl tosylate,[38,39] coupling of the aryl Grignard reagent and the alkyl bromide,[40,41] coupling of the aryl and alkyl magnesium bromides,[42] Wurtz-Fittig coupling of the two bromides[43] and coupling of the aryl sodium[44] or lithium[45,46] derivatives with the alkyl bromide. However, none of these reactions succeeded in producing the desired product (22) in quantity sufficient to isolate. The predominant reaction in all cases was the elimination of the elements of p-toluenesulfonic acid or hydrobromic acid from the alkyl group to form 2-methylpenta-2,4-diene and 3-methylbenzofuran. One fact concerning the coupling of the aryl magnesium bromide and the alkyl tosylate should be mentioned. The classical procedure was developed by Marvel[38,39] as a method of adding a 3-chloropropyl group to a Grignard reagent. It was found if tetrahydrofuran was used as the solvent instead of ether no coupling between phenyl magnesium bromide and the tosylate of 3-chloropropanol was observed. However, even if the tetrahydrofuran, necessary for the formation of the Grignard reagent of 3-methyl-5-bromobenzofuran, was then replaced with ether, no coupling occurred. By far the largest amount of coupling, still less than 10%, occurred between the aryl lithium compound and the alkyl bromide.[45] Even if the coupling between the aryl lithium or aryl sodium compounds and the alkyl bromide would have been successful, there is a possibility that, at least in part, the 2-alkyl-benzofuran would have been formed. The acidity of the C-2 proton of furan[47] (stronger acid than triphenylmethane) and

benzofuran[48-51] is well established and the initially formed 3-methyl-5-lithiobenzofuran could have reacted with unchanged 3-methyl-5-bromobenzofuran to form 2-lithio-3-methyl-5-bromobenzofuran and 3-methylbenzofuran. That the Grignard reagent does not undergo this reaction was shown by formation of the Grignard followed by carbonation to give 3-methyl-5-benzofurancarboxylic acid.



A five carbon portion of the side chain was formed by protecting the carbonyl of methyl heptenone (28) as the ethylene ketal

followed by ozonolysis of the double bond to form the ethylene ketal of levulinaldehyde (29). Addition of the above aldehyde to the Grignard reagent from 3-methyl-5-bromobenzofuran gave the benzylic alcohol (30). The low yield (28%) of this Grignard reaction may be due, at least in part, to the fact that benzofurans are able to form a 1:1 complex with



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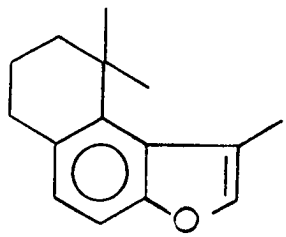


(34)

Grignard reagents.[52] Catalytic hydrogenolysis of the benzyl alcohol was accompanied by spontaneous hydrolysis of the ketal to give the ketone (31) which was treated with methyl magnesium iodide to give the tertiary alcohol (32). Dehydration of the alcohol with formic acid gave a mixture of tricyclic products, (33) and (34), the result of electrophilic attack by the intermediate carbonium ion on the aromatic ring. Although this facile ring closure could not be avoided entirely, a more satisfactory dehydration was accomplished with phosphorus oxychloride in pyridine which provided a mixture of the cyclic products and the two isomeric olefins. The desired product, furanoventalinene A (22), was separated by chromatography on silver nitrate impregnated silicic acid.

The NMR spectrum (Fig. 23) was identical in all respects with the spectrum of naturally occurring furanoventalinene (Fig. 20) in the

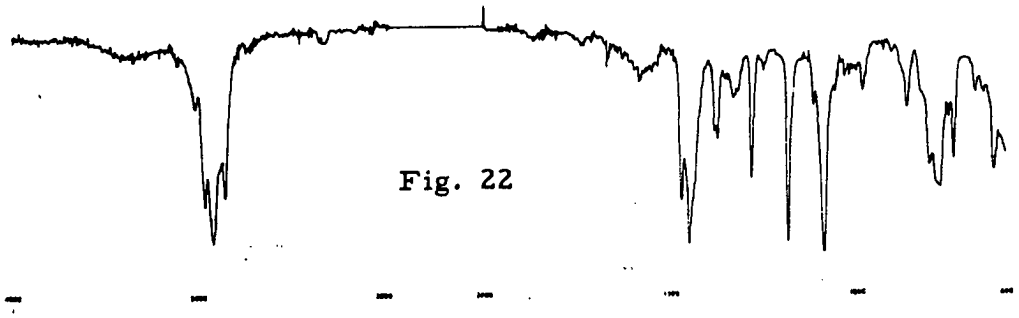


Fig. 22

3-Methyl-5-(4'-methyl-3'-pentenyl)benzofuran

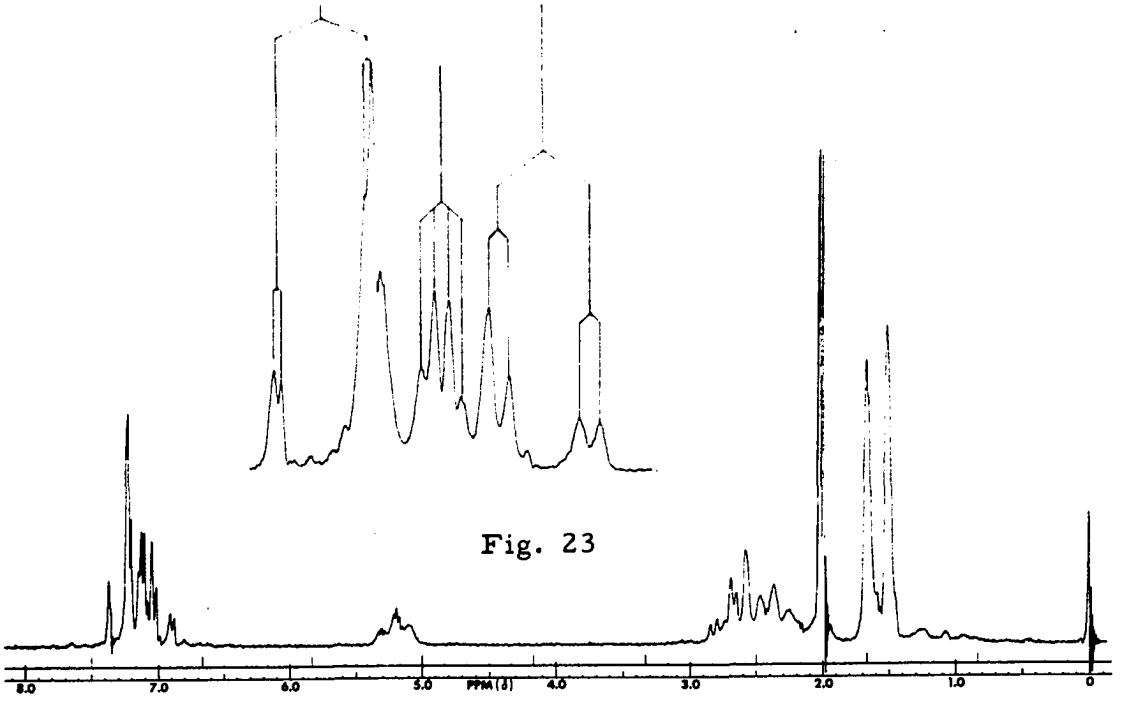


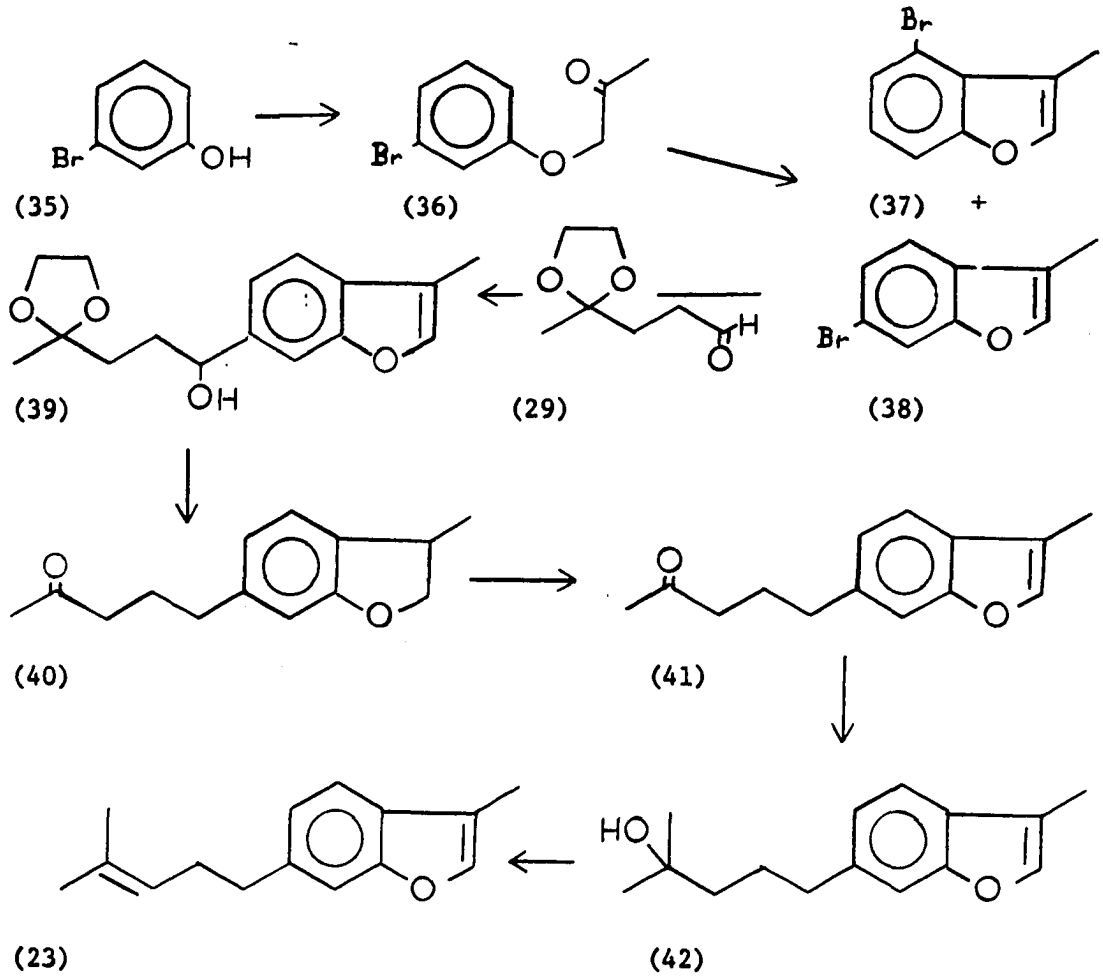
Fig. 23

region of δ 1 to 6, but the aromatic region, insets of Figs. (20) and (23), was slightly different. In particular, the J values, J_o = 8.2, J_m = 1.8, and J_p = 0.6 cps were not the same as those of the naturally occurring furanoventalinene, J_o = 8.0, J_m = 1.2, and J_p = 0.6 cps. The IR spectra (Figs. 19 and 22) were very different, particularly in the "fingerprint" region. The most intense band which was different, assigned as an aromatic absorption, occurred at 1183 cm^{-1} in furanoventalinene A and at 1129 cm^{-1} in the naturally occurring furanoventalinene.

Synthesis of furanoventalinene B (23), 3-methyl-6-(4'-methyl-3'-pentenyl)benzofuran, followed much the same path. O-Alkylation of m-bromophenol (35) gave m-bromophenoxyacetone (36). Cyclodehydration with polyphosphoric acid gave a mixture of 3-methyl-4-bromobenzofuran (37) and 3-methyl-6-bromobenzofuran (38) in a ratio of approximately 2.5 to 1. The separation of this mixture was accomplished by a combination of fractional distillation and column chromatography. Identification of the two products of this mixture was made from the analysis of their NMR spectra. The NMR spectrum of the desired product, the minor component (36), was readily analyzed by a first order interpretation. In addition to a doublet at δ 1.86 (3H) J = 1.1 cps, due to the C-3 methyl, the NMR spectrum (neat) displayed a double doublet at δ 6.84 (1H), J_o = 8.2 and J_p = 0.5 cps, due to the C-4 aromatic proton. The C-2 furan proton appeared as a quartet at δ 7.06 (1H), J = 1.1 cps. The double doublet at δ 7.10 (1H), J_o = 8.2 cps and J_m = 1.6 cps, was

assigned as the C-5 aromatic proton while the double doublet at δ 7.38 (1H) J_m = 1.6 and J_p = 0.5 cps, was assigned as the C-7 aromatic proton. Thus with all three types of aromatic coupling present, ortho, meta, and para, a 1,2,4-trisubstituted aromatic system was confirmed. A first order interpretation of the spectrum of the major component, 3-methyl-4-bromobenzofuran (37) failed to explain all of the signals. Additional signals were apparently due to secondary splitting and the J values given here would only be the apparent J values. In addition to a doublet at δ 2.14 (3H), J = 1.1 cps, due to the C-3 methyl, the NMR spectrum (neat) of 3-methyl-4-bromobenzofuran, displayed a doubled double doublet at δ 6.77 (1H), J_o = 8.2, J_o = 7.8 and J = 0.4 cps, assigned as the C-6 aromatic proton. The additional coupling, J = 0.4 cps, was explained as "straight zig-zag" coupling[53] between the C-2 and C-6 protons. This coupling is similar to the crossring "zig-zag" coupling between protons on C-3 and C-7 of benzofuran observed by Foster and Elvidge.[54] The cross-ring coupling was also observed in the C-2 furan proton which appeared as a doubled quartet at δ 7.03 (1H), J = 1.1 and 0.4 cps. The double doublets at δ 7.12 (1H), J_o = 8.2 and J_m = 1.4 cps, and δ 7.17 (1H), J_o = 7.8 and J_m = 1.4 cps, were assigned as the C-5 and C-7 aromatic protons although it was not possible to distinguish between the two. The fact that there were clearly two ortho and one meta couplings established the structure as 3-methyl-4-bromobenzofuran (37). These assignments are consistent with the observation of the effect of the proximity of the bromine on the chemical shift of the C-3 methyl. In the 3-methyl-4-bromo- compound (37), the methyl signal appears at δ 2.14, whereas in the 3-methyl-6-bromo- compound (38), the methyl signal appears at δ 1.86.

The ethylene ketal of levulinaldehyde (29) was condensed with the Grignard reagent of 3-methyl-6-bromobenzofuran (38) to give the benzyl alcohol (39). Hydrogenation, in ethyl acetate as before, took place



selectively at the furan double bond and did not affect the alcohol or ketal functions as in the previous example. Rehydrogenation in acetic acid accomplished the desired side chain transformation, giving the saturated ketone (40). Dehydrogenation on 5% palladium on charcoal[55]

formed the benzofuran (41) which, as before, was converted to the tertiary alcohol (42) with methyl magnesium iodide. Dehydration with phosphorus oxychloride led to the same type mixture as before of cyclic products and the two double bond isomers. The desired trisubstituted isomer, furanoventalinene B (23), was separated by a combination of chromatography on silver nitrate impregnated silicic acid and preparative gas chromatography. The IR and NMR spectra were identical in all respects with those of naturally occurring furanoventalinene (Figs. 19 and 20). The NMR data are assigned in Table 2.

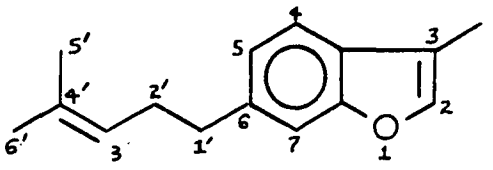


TABLE 2

NMR Assignments of Furanoventalinene

Signal (δ)	Multiplicity	Protons	J Value (cps)	Assignment
1.50	d	3	0.7	C-5' methyl
1.64	d	3	1.0	C-6' methyl
1.97	d	3	1.1	C-3 methyl
2.30	m	2		C-2' methylene
2.51	1/2 of A_2B_2	2		C-1' methylene
5.19	m	1	7.5, 1.0, 0.7	C-3' proton
6.98	dd	1	8.0, 1.2	C-5 proton
7.13	q	1	1.1	C-2 proton
7.25	dd	1	1.2, 0.6	C-7 proton
7.29	dd	1	8.0, 0.6	C-4 proton

EXPERIMENTAL

All melting points are uncorrected. All solvents were redistilled before use. Tetrahydrofuran was distilled from lithium aluminum hydride. Chromatographic supports were alumina (Alcoa F-20), Florisil (Floridin Co, 100/200 mesh), and silicic acid (Mallinckrodt, 100 mesh). Silver nitrate impregnated silicic acid was prepared using a modification of the procedure of Norin and Westfelt.[21] Silicic acid (450 g) was slurried into a solution of silver nitrate (125 g) in water (750 ml). As much water as possible was removed under vacuum on a rotary evaporator and the residual water was removed by heating at 110° for 48 hours. The white solid was sieved through a 100 mesh sieve.

Thin layer chromatography was performed on 5 x 20 cm glass plates coated with Merck (Darmstadt) silica gel H or silver nitrate impregnated silica gel H.[56] The silica gel H plates were placed in iodine vapor for visualization of the chromatogram. Silver nitrate impregnated silica gel H plates were visualized by spraying with 2,7-dichlorofluorescein and then exposing the plate to UV light.

Gas chromatographic analyses were performed on a Barber-Colman, Model 20 or an Aerograph Autoprep, Model A-700. The IR spectra were recorded on a Beckman IR-8 spectrophotometer. The IR spectra were run in carbon tetrachloride solutions in 0.1 mm cells, as a thin film

run in carbon tetrachloride solutions in 0.1 mm cells, as a thin film between two salt discs or as potassium bromide pellets.

NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal reference. Samples were run as neat liquids or as solutions in varying concentrations in carbon tetrachloride or deuteriochloroform. Chemical shifts are reported in δ-values (p.p.m. from TMS) and are followed by the multiplicity of the signals and the corresponding coupling constants. The multiplicities are denoted by the symbols: s, singlet; d, doublet; dd, double doublet; ddd, doubled double doublet; t, triplet; q, quartet; dq, doubled quartet; m, multiplet.

Analyses were carried out by the Alfred Bernhardt Laboratories, Mulheim, Germany. Mass spectra were kindly provided by Dr. R. Grigsby, Continental Oil Company, Ponca City, Oklahoma.

A. Eunicea mammosa

Isolation of (+)-β-Elemene. Air dried Eunicea mammosa (1.5 kg), collected at Bimini in 1962, was leached twice with 2.5 liter portions of pentane. The solvent was removed under vacuum on a rotary evaporator and the residual black oil (25 g) was distilled through a falling film molecular still (Nester/Faust) at 120°/0.10 mm. The yellow distillate (11 g) was chromatographed in hexane through 375 g of Florisil. Gas chromatography on a 6' x 1/8" 5% SE-30 column indicated the colorless hydrocarbon portion (1.6 g, 0.11%), found in the early fractions was essentially (99%) a single component. Further purification was achieved

by preparative gas chromatography on a 20' x 3/8" 30% SE-30 on 45/60 Chromsorb P column. The effluent was collected under hexane at room temperature. The solvent was removed under vacuum on a rotary evaporator leaving a colorless oil (1.10 g) which gas chromatography (6' x 1/8" 5% SE-30 on Gaschrom Z) indicated was a single component, n_D^{25} 1.4910, d_4^{25} 0.8852, $[\alpha]_D^{25}$ + 15.1° (neat), m.w. 204 (m.s.); (Lit.[4] n_D^{20} 1.4911, d_4^{20} 0.8869, $[\alpha]_D^{20}$ - 15.4°). The IR spectrum (film) exhibited bands at 1643 cm^{-1} (double bond), 908 cm^{-1} (vinyl) and 887 cm^{-1} (terminal methylene). The NMR spectrum (neat) showed signals at δ 0.98, s, 3H (quaternary methyl); 1.17, s, 6H (vinyl methyl); 4.75, m, 6H (terminal methylene) and 5.87, q, 1H (vinyl hydrogen).

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.16; H, 11.70.

NMDR of (+)-β-Elemene. The lone non-terminal vinyl proton appearing as a quartet at δ 5.87 was shown to be coupled with the proton appearing as a quartet at δ 5.02 and with the unresolved multiplet centered at δ 4.86 responsible for the fine detail on the downfield side of the broad band at δ 4.58-4.92.

Chromatography of (+)-β-Elemene on Silicic Acid. Air dried Eunicea mammosa (5 kg), collected at Bimini in 1962, was leached twice with 5 liters of pentane. The solvent was removed under vacuum on a rotary evaporator and the residual black oil (70 g) was distilled through a falling film molecular still (Nester/Faust) at 120°/0.1 mm. The yellow distillate (35 g) was chromatographed in hexane on 875 g of Florisil. The colorless oil (12.30 g), 99% pure by gas chromatographic analysis

(SE-30), which was eluted in the early fractions was rechromatographed in hexane on 750 g of silicic acid.

Fractions 28-48 (3.60 g) were a mixture of two hydrocarbons. Preparative gas chromatography (20' x 3/8" 30% SE-30 on 45/60 Chromsorb P) of fractions 28-30 resulted in a reasonably pure sample (85%) of (-)-β-selinene (0.60 g) n_D^{25} 1.5035, d_4^{25} 0.9115, $[\alpha]_D^{25}$ - 20.4° (neat), (Lit.[4] n_D^{20} 1.5025, d_4^{20} 0.9140, $[\alpha]_D^{20}$ + 50.0°). The IR spectrum (film) exhibited bands at 1647 cm^{-1} (double bond) and 880 cm^{-1} (terminal methylene), (Lit.[8] 1644 and 882 cm^{-1}). The NMR spectrum (neat) showed signals at δ 0.72, s, 3H (quaternary methyl); 1.71, s, 3H (vinyl methyl); 4.60-4.80, m, 2H (terminal methylene) and weak signals due to impurity at 0.81, s, and 5.35, broad s.

Fractions 40-44 contained an impure sample (75%) which was identified as (+)-α-selinene (0.34 g) by its IR and NMR spectra. The IR spectrum (film) exhibited bands at 1645 cm^{-1} (double bond), 882 cm^{-1} (terminal methylene) and 845 and 790 cm^{-1} (trisubstituted double bond), (Lit.[9] 1644, 885, 847 and 792 cm^{-1}). The NMR spectrum (neat) showed singlets at δ 0.81, s, 3H (quaternary methyl); 1.74, s, 6H (vinyl methyl); 4.74, broad s, 2H (terminal methylene); 5.35, broad s, 1H (vinyl hydrogen) and a weak signal due to an impurity at 0.72.

Fractions 49-91 were combined (1.72 g) and submitted to preparative gas chromatography (20' x 3/8" 30% SE-30 on 45/60 Chromsorb P) providing a sample of pure (+)-β-elemene (1.20 g).

Isolation of (+)-β-Elemene from Zooxanthellae. Intact zooxanthellae (13.2 g), isolated by blendor maceration and sedimentation

of fresh Eunicea mammosa collected at Bimini in 1966, were oven dried (65°) and extracted using a Soxhlet with hexane. The solvent was removed under vacuum on a rotary evaporator and the residual oil (2.5 g) was distilled through a Hickman type still.* Fraction 1 (50-80°/2 mm), a colorless oil (550 mg), was chromatographed in hexane on 25 g of Florisil. Gas chromatography (6' x 1/8" 5% SE-30 on 80/100 Gaschrom Z) of the hydrocarbon portion (479 mg), which was eluted in the early fractions, indicated two major components. The first component had the same retention time as (+)-β-elemene. The IR spectrum (film) of the mixture exhibited bands at 1643 cm^{-1} (double bond) and 885 cm^{-1} (terminal methylene) due to β-elemene in addition to bands at 1647 cm^{-1} (double bond), 882 cm^{-1} (terminal methylene) and 842 cm^{-1} (trisubstituted double bond) due to the other hydrocarbon. The NMR spectrum (neat) showed signals at δ 0.97, s, (quaternary methyl); 1.69, s, (vinyl methyl); 4.75-5.05, m, (terminal methylene) and 5.80, C of ABC (vinyl hydrogen) due to β-elemene as well as signals at 1.67, s (vinyl methyl), 4.50-4.85, m (terminal methylene) and 4.95, m (vinyl hydrogen) due to the other hydrocarbon.

Chromatography in hexane on 25 g of Florisil of fraction 2 (80-100°/2 mm) of the distillation (299 mg) resulted in 120 mg of hydrocarbon in the early fractions. The hydrocarbon portions of fractions 1 and 2 of the distillation were combined (617 mg, 4.7%) but before any further work could be accomplished, the sample had deteriorated as a result of air oxidation and polymerization. The second, unknown,

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*This experiment was carried out by Dr. L. S. Ciereszko.

hydrocarbon component was attacked more extensively than β-elemene as shown by the change in their relative concentrations in the residual hydrocarbon after partial decomposition. Chromatography of the oxidized mixture led to isolation of a small amount of a crystalline ketone which was not characterized further.*

B. Pseudoplexaura porosa

Isolation of Sesquiterpene Hydrocarbon Fraction. The tips of air dried Pseudoplexaura porosa (8.7 kg), collected at Bermuda in 1963, were leached twice with 10 liters of cold hexane. The solvent was removed on a rotary evaporator under vacuum leaving a black oil (710 g). Distillation at 110°/0.2 mm on a falling film molecular still (Nester/Faust) of part (463 g) of this oil gave a clear yellow distillate (31.6 g) which was chromatographed on 100 g of alkaline alumina (Alcoa F-20) in hexane. The early fractions (1-3, 100 ml each) contained 22.3 g of colorless hydrocarbon. Gas chromatography, 10' x 3/8" 25% LAC-1-R-296 on 80/100 Gaschrom Z, showed a mixture of at least three major components. For identification purposes, these were numbered, A-C. Component A was approximately 10%, B-50% and C-35% of the total hydrocarbon mixture.

The hydrocarbon portion (21.8 g) was distilled on an 18" Nester/Faust spinning band column rated at 23 theoretical plates. The distillate fractions were analyzed by gas chromatography (6' x 1/8" 5% Carbowax 20M on 80/100 Gaschrom Z). No accurate boiling point could be

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*This experiment was carried out by R. E. Hopla.

recorded because of the low boil-up rate used. The results of the distillation are shown in Table 3.

TABLE 3

Distillation of Pseudoplexaura porosa Oil

Fractions	Weight	Components Present	Major Component
1-9	4.49 g	A and B	B
10-15	4.42 g	B and C	B
16-17	0.66 g	B and C	Equal
18-20	1.99 g	B and C	C
21-23	1.95 g	C	
24-27	2.54 g	Several	
Pot residue		Oxidation and polymerization products	

Gas chromatography (6' x 1/8" 5% Carbowax 20M on 80/100 Gaschrom Z and 10' x 3/8" 25% LAC-1-R-296 on 80/100 Gaschrom Z) indicated fractions 21-23 were essentially pure (99%) component C, n_D^{25} 1.4983, d_4^{25} 0.9205, $[\alpha]_D^{25}$ + 10.6 (neat), m.w. 204 (m.s.). The IR spectrum (film) showed significant bands at 3040, 1643 and 872 cm^{-1} (terminal methylene) and the NMR spectrum (neat) exhibited signals at δ 0.68, s, 3H (quaternary methyl); 0.85, d, J = 5.5 cps, 6H (isopropyl) and 4.58, m, 2H (terminal methylene). The hydrocarbon was

identified as β-ylangene [Lit.[12] n_D^{20} 1.5000, IR (film) 1640 and 875 cm^{-1}].

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.30; H, 11.70.

Fraction 7 was a mixture of components A and B which gas chromatography, as above, indicated were in a ratio of approximately 1:5. The IR spectrum (film) exhibited significant bands at 3080, 1650, and 862 cm^{-1} (terminal methylene). The NMR spectrum (neat) showed a weak signal at δ 5.19, m, (vinyl hydrogen) and signals at 4.52, narrow m, 1H and 4.71, narrow m, 1H (terminal methylene).

C. Pseudopterogorgia americana

Isolation of Sesquiterpene Hydrocarbon Fraction of Pseudopterogorgia americana.* Air dried Pseudopterogorgia americana (2.5 kg), collected at Bermuda in 1962, was extracted with pentane and then ether in a continuous extractor.[57] The black oil (124 g), remaining after removal of the solvent from the combined extracts, was saponified by heating at reflux for 2 hours with a mixture of 150 ml of 30% potassium hydroxide and 450 ml of methanol. The bulk of the methanol was replaced with water and the nonsaponifiable material was extracted from the basic solution by continuous extraction with ether. The ethereal solution was washed with water, dried over sodium sulfate and concentrated under vacuum on a rotary evaporator leaving a brown oil (65 g). Chromatography on silicic acid in hexane resulted in a colorless oil (24 g) which

*This experiment was performed by Dr. L. S. Ciereszko.

was distilled through a short path still at 85-90°/0.05 mm (22.6 g, 0.9%).

Isolation of the Individual Hydrocarbons of Pseudopterogorgia americana. Chromatography of the hydrocarbon mixture from above (9.0 g) on 900 g of silver nitrate impregnated silicic acid in hexane provided, in fractions 46-67 (50 ml each) a sample of a hydrocarbon (0.553 g, 7.6% of total eluted) identified as (+)-9-aristolene, n_D^{25} 1.4975, d_4^{25} 0.9249, $[\alpha]_D^{25}$ + 80.9 (neat), m.w. 204 (m.s.); Lit.[22] n_D^{18} 1.5040, d_4^{18} 0.9331, $[\alpha]_D^{18}$ + 68°). Thin layer chromatography (R_f 0.55, hexane, silicic acid-silver nitrate) indicated this was a pure compound. The IR spectrum (film) showed significant bands at 3040 cm^{-1} (cyclopropane) and 1669, 810 and 776 cm^{-1} (trisubstituted double bond). The NMR spectrum (neat) exhibited signals at δ 5.07, broad m, 1H (vinyl hydrogen); 2.12, broad m, 4H (allylic protons); 1.09, s, 3H (quaternary methyl); 1.04, s, 3H (quaternary methyl); 1.02, s, 3H (quaternary methyl); 0.94, d, J = 6 cps, 3H (secondary methyl) and 0.65, m, 2H (cyclopropane). No suitable analysis could be obtained because of rapid air oxidation.

On continued elution with hexane, fractions 82-135, (100 ml each) provided a sample of a hydrocarbon (1.813 g, 24.9%) identified as (-)-1(10)-aristolene, n_D^{25} 1.5005, d_4^{25} 0.9198, $[\alpha]_D^{25}$ - 78.5° (neat), m.w. 204 (m.s.); (Lit.[24] n_D^{20} 1.5051, d_4^{20} 0.9340, $[\alpha]_D^{20}$ + 81.8°). Thin layer chromatography (R_f 0.44, hexane, silicic acid-silver nitrate) indicated this was a pure compound. The IR spectrum (film) showed significant bands at 3040 cm^{-1} (cyclopropane) and 1669 and 832 cm^{-1} (trisubstituted double bond). The NMR spectrum (neat) exhibited signals at δ 5.22, dd, J = 3.6 and 2.2 cps, 1H (vinyl hydrogen); 1.04, s, 3H (quaternary methyl); 1.00, s, 3H (quaternary methyl); 0.96, s, 3H (quaternary methyl);

0.96, d, J = 7 cps, 3H (secondary methyl) and 0.59, m, 2H (cyclopropane).

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.01; H, 11.79.

Fractions 237-246, 171 mg, eluted with hexane-benzene (3:1), were a mixture of two compounds as indicated by thin layer chromatography [R_f 0.47, 0.41, hexane-benzene (1:1) silicic acid-silver nitrate]. Fractions 247-255, hexane-benzene (3:1), (0.615 g, 8.5%) contained a hydrocarbon identified as (+)-γ-maaliene, n_D^{25} 1.4992, d_4^{25} 0.9230, $[\alpha]_D^{25}$ + 11.6° (neat), m.w. 204 (m.s.); (Lit.[27] n_D^{25} 1.5008). Thin layer chromatography [R_f 0.41, hexane-benzene (1:1), silicic acid-silver nitrate] indicated this was a pure compound, but later it was shown to have 10% impurity by gas chromatography (LAC-1-R-296).[29] The IR spectrum (film) exhibited significant bands at 3020 cm^{-1} (cyclopropane) and 3080, 1647 and 879 cm^{-1} (terminal methylene). The NMR spectrum (neat) showed signals at δ 4.79, m, 2H (terminal methylene); 1.02, s, 3H (quaternary methyl); 0.90, s, 3H (quaternary methyl); 0.73, s, 3H (quaternary methyl) and 0.67, m, 2H (cyclopropane).

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.20; H, 11.79.

Elution with ethyl acetate, fractions 331-341, produced a white solid mixed with an oil. Filtration and recrystallization (acetone-hexane) resulted in a white crystalline solid (0.535 g, m.p. 132.5-133.5°). The IR spectrum (KBr) showed significant bands at 1646, 1601, 888, 878, and 820 cm^{-1} (double bond) and 1385 cm^{-1} (nitrate).

Anal. Calcd. for $C_{15}H_{24}\cdot AgNO_3$: C, 48.14; H, 6.46, Ag, 28.82. Found: C, 48.03, H, 6.46,; Ag, 28.88

The filtrate and supernatant liquids were combined and rechromatographed on Florisil (50 g) in hexane. The colorless oil (3.735 g, 51.4%) resulting from the chromatography could not be identified as any known hydrocarbon and was called (+)-β-gorgonene, n_D^{25} 1.5010, d_4^{25} 0.9108, $[\alpha]_D^{25}$ + 13.9° (neat), m.w. 204 (m.s.). The IR spectrum (film) exhibited bands at 3070, 1645, 888 and 878 cm^{-1} (two terminal methylenes). The NMR spectrum (neat) showed signals at δ 4.66, m, 4H (terminal methylene); 1.55, d, J = 1.0 cps, 3H (vinyl methyl) and 0.79, s, 3H (quaternary methyl).

Osmium Tetroxide Oxidation of (+)-γ-Maaliene. The procedure used was that due to Büchi.[28] (+)-γ-Maaliene (100 mg, 0.49 mmoles) was dissolved in 1 ml of dry pyridine and cooled in an ice bath. Osmium tetroxide (200 mg, 0.79 mmoles) was dissolved in 4 ml of pyridine, cooled to an ice bath and added to the olefin. The reaction mixture was allowed to stand at room temperature for four days and then was refluxed for four hours with a mixture of 1.5 g mannitol, 1.5 g potassium hydroxide, 3.8 ml water, 3.8 ml benzene and 11.3 ml ethanol. The mixture was diluted with 100 ml of water and extracted twice with 50 ml portions of hexane. The hexane solution was dried over sodium sulfate and the solvent removed on a rotary evaporator under vacuum leaving a white solid (103 mg) which was chromatographed on Florisil (10 g) in benzene-ethyl acetate (8:2). Fractions 3-7, 10 ml each, contained a white crystalline solid (92 mg) which was recrystallized from benzene-hexane (63 mg, 55%) m.p. 141-142° (sublimed), $[\alpha]_D^{25}$ - 24.8° (c, 6.3 chloroform). The IR

spectrum (KBr) showed significant bands at 3440, 1045, 1026 and 1012 cm^{-1} (hydroxyl). The NMR spectrum ($CDCl_3$) exhibited signals at δ 3.75, broad s, 2H ($-O-CH_2-$);1.05, s, 3H (quaternary methyl); 0.95, s, 3H (quaternary methyl); 0.82, s, 3H (quaternary methyl) and 0.61, m, 2H (cyclopropane).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 75.58; H, 10.99. Found: C, 75.32; H, 10.74.

A sample of (+)-γ-maalidiol, provided by Dr. Büchi, had m.p. 138-140° (sublimed), $[\alpha]_D^{25}$ + 24.4° (c, 5.7 chloroform). The IR spectra (KBr) of this sample and of the (-)-γ-maalidiol prepared above were identical in all respects. A sample of d,l-γ-maalidiol was prepared by dissolving 0.6 mg of each diol in acetone and removing the solvent, m.p. 126-128° (sublimed).

D. Gorgonia ventalina

Isolation of Furanoventalinene. Air dried Gorgonia ventalina (2.5 kg), collected at Bermuda in 1961, was extracted in a percolator extractor[57] with pentane.* After removal of the solvent under vacuum, the residual black oil (450 g) was continuously steam distilled with the distillate being continuously extracted with ether. After 12 days, a yellow oil (10 g) had been collected in the ether. The early fractions (6-11, 30 ml each) of a chromatography on Florisil (125 g) in hexane contained a pale yellow oil (2.687 g) which thin layer chromatography (hexane, silicic acid) indicated was composed of one major portion

*The extraction was performed by L. S. Ciereszko.

(R_f 0.96), two minor components (R_f 0.90 and 0.51) and several trace components (R_f 0.83, 0.62, 0.19, 0.12, 0.09 and 0.03). Continued elution with hexane, fractions 12-19, resulted in a pale yellow oil (0.551 g) which according to thin layer chromatography (hexane-silicic acid) consisted of one major component (R_f 0.51), two minor components (R_f 0.96 and 0.03), and two trace components (R_f 0.12 and 0.09). Further elution with hexane, fractions 20-24, gave a pale yellow oil (0.869 g) which thin layer chromatography (hexane, silicic acid) indicated contained one major component (R_f 0.03) and two minor components (R_f 0.51 and 0.96). Thin layer chromatography of the same sample on silicic acid in hexane-benzene (1:1) indicated two major components (R_f 0.72 and 0.61) and several trace components (R_f 0.96, 0.85, 0.78, 0.49, and 0.35).

Elution with benzene, fractions 25-35, gave a pale yellow oil (2.174 g) which thin layer chromatography (hexane-benzene, 1:1, silicic acid) indicated contained one major component (R_f 0.17), one minor component (R_f 0.49) and several trace components (R_f 0.72, 0.61, and 0.35). Continued elution with benzene, fractions 36-48, gave a white solid (0.772 g) which thin layer chromatography (benzene, silicic acid) indicated was one major component (R_f 0.22) and several trace components (R_f 0.71, 0.47, and 0.37). Further elution with benzene, fractions 49-57, gave a yellow oil (0.302 g) which thin layer chromatography (benzene-ethyl acetate, 9:1, silicic acid) indicated was primarily two components (R_f 0.09 and 0.00) with several trace components, (R_f 0.93, 0.84, 0.66, 0.55, 0.44, 0.38, 0.21, and 0.17).

Elution with ethyl acetate, fractions 58-61, gave a yellow oil (0.846 g) which thin layer chromatography (benzene-ethyl acetate, 9:1,

silicic acid) indicated contained several major components (R_f 0.93, 0.84, 0.44, 0.09, and 0.00) and several minor components (R_f 0.66, 0.38, 0.21 and 0.17). Continued elution with ethyl acetate, fractions 62-76, produced a yellow oil (0.173 g) which thin layer chromatography (benzene-ethyl acetate, 9:1, silicic acid) indicated contained two major components (R_f 0.09 and 0.00) and three minor components (R_f 0.93, 0.33, and 0.21).

Elution with methanol, fractions 77-85, gave a yellow solid (1.402 g) which thin layer chromatography (benzene-ethyl acetate, 8:2, silicic acid) indicated was essentially two components (R_f 0.31 and 0.00).

Fractions 36-48 were combined and recrystallized from hexane to give a white solid, m.p. 52-52.5 The IR spectrum ($CDCl_3$) showed signals at 3320 and 1060 cm^{-1} (hydroxyl). The compound was identified as cetyl alcohol, (Lit.[58] m.p. 50°). It was shown to be identical by gas chromatography (6' x 1/8" 20% LAC-1-R-296) when compared with an authentic sample.

Anal. Calcd. for $C_{16}H_{34}O$: C, 79.26; H, 14.14. Found: C, 79.15; H, 14.04.

The following samples were submitted to bioassay tests for activity against tuberculosis and histoplasmosis.* None of the samples showed any activity against histoplasmosis but sample B showed activity against tuberculosis at a level of 1,000 µg/ml. There was 100% kill of tubercle bacilli in 10 samples.

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*Biological testing was performed by Dr. H. W. Larsh, University of Oklahoma, and J. Bohanan, Missouri State Sanitarium.

Sample	Fractions
A	8-11
B	12-19
C	20-24
D	25-35
E	36-48
F	49-57
G	58-61
H	77-84

It was decided that the best chance of isolating the active component would be to isolate the major component of sample B (R_f = 0.51, hexane, silicic acid). In addition to being the major component of sample B, this same compound (R_f = 0.51) was a minor component of sample A. In order to obtain the largest possible sample, the remainder of both A and B, fractions 8-19, after bioassay were combined and were chromatographed on silicic acid (200 g) in hexane. Fractions 3-17, 100 ml each, contained a colorless oil (0.370 g) and according to thin layer chromatography (hexane, silicic acid) consisted of one major component (R_f 0.96) and two minor components (R_f 0.90 and 0.83). Continued elution with hexane gave a sample, fractions 34-71, which contained a colorless oil (0.538 g) and according to thin layer chromatography (hexane, silicic acid) consisted of one major component (R_f 0.51), one minor component (R_f 0.62) and one trace component (R_f 0.01). The oil was chromatographed on silver nitrate impregnated silicic acid (40 g) in hexane-benzene (9:1). Fractions 1-3, 40 ml each, contained a colorless oil (90 mg) which thin layer chromatography (hexane-benzene, 1:1, silver nitrate-silicic acid) indicated was composed

of one major component (R_f 0.35) and one minor component (R_f 0.30). Fractions 4-11 contained a colorless oil (360 mg) which thin layer chromatography (hexane-benzene, 1:1, silver nitrate-silicic acid) also indicated was composed of one major component (R_f 0.30) and one minor component (R_f 0.35). Fractions 35-45 contained a white solid (47 mg) identified as cetyl alcohol (R_f 0.17, hexane-benzene, 1:1, silicic acid).

Rechromatography of fractions 4-11 on silver nitrate impregnated silicic acid (40 g) in hexane-benzene (19:1) gave a sample (from fractions 7-24, 40 ml each) of a colorless oil (331 mg) which showed a single spot on thin layer chromatography (R_f 0.30, hexane-benzene, 1:1, silver nitrate-silicic acid). The sample was filtered through Florisil (15 g) in hexane to give an analytical sample (317 mg) identified as 3-methyl-6-(4'-methyl-3'-pentenyl)benzofuran, m.w. 214 (m.s.), $[\alpha]_D^{25}$ 0.00 + 0.3°. The UV spectrum showed maxima at 249 mμ (ε = 16,000), 282 mμ (ε = 4,200) and 287 mμ (ε = 6,200). The IR spectrum (film, Fig. 20) exhibited bands at 3030 and 1129 cm^{-1} (aromatic), 1084 cm^{-1} (ether) and 808 and 796 cm^{-1} (trisubstituted double bond). The NMR spectrum (neat, Fig. 21) showed signals at δ 1.50, d, J = 0.7 cps, 3H (C-5' vinyl methyl); 1.64, d, J = 1.0 cps, 3H (C-6' vinyl methyl); 1.97, d, J = 1.1 cps, 3H (C-3 methyl); 2.30, m, 2H (allylic methylene); 2.51, A_2 of A_2B_2, 2H (benzylic methylene); 5.19, m, J = 0.7, 1.0 and 6.5 cps (vinyl hydrogen); 6.98, dd, J_o = 8.0 cps and J_m = 1.2 cps, 1H (C-5 aromatic hydrogen); 7.13, q, J = 1.1 cps, 1H (C-2 hydrogen); 7.25, dd, J_m = 1.2 cps and J_p = 0.6 cps, 1H (C-7 aromatic hydrogen); 7.29, dd, J_o = 8.0 cps and J_p = 0.6 cps, 1H (C-4 aromatic hydrogen).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.79; H, 8.33.

NMDR of Furanoventalinene. The vinyl hydrogen, appearing as a triplet with additional fine splitting at δ 5.19, could be shown to be coupled with both vinyl methyls appearing as narrow doublets at δ 1.50 and 1.64. Irradiation at δ 5.19 caused the vinyl methyls to collapse to singlets and irradiation at δ 1.57 causing the triplet to lose the fine splitting. The vinyl hydrogen could also be shown to be coupled with the allylic methylene at δ 2.30. Irradiation at δ 2.30 caused the triplet with fine splitting at δ 5.19 to collapse to a singlet with additional fine splitting. The doublet at δ 1.97 (C-3 methyl) could be shown to be coupled with the quartet at δ 7.13 (C-2 hydrogen). Each collapsed to a sharp singlet when the other was irradiated.

Hydrogenation of Furanoventalinene. Furanoventalinene (50 mg, 0.23 mmoles) was hydrogenated at atmospheric pressure in acetic acid (20 ml) over Adams catalyst (10 mg). The sample took up two molar equivalents of hydrogen. After filtering and removing the solvent under vacuum on a rotary evaporator, the tetrahydrofuranoventalinene was chromatographed on silver nitrate impregnated silicic acid (5 g) in hexane. Fractions 3-5, (10 ml each) contained only a trace of colorless oil. Fractions 8-26 gave a very pale yellow oil (26 mg). The remainder of the sample was polar material. Chromatography of the pale yellow oil on Florisil (5 g) in hexane gave a colorless oil (21 mg, 41%). The NMR spectrum (CCl_4) showed signals at δ 6.75, m, 3H (aromatic hydrogens); 4.61, dd, J = 8.5 and 7.5 cps, 1H (C-2 hydrogen); 4.00, dd, J = 7.5 and

7.0 cps, 1H (C-2 hydrogen); 3.44, m, J = 8.5, 7.0 and 6.5 cps, 1H (C-3 hydrogen); 2.51, t, J = 7.0 cps, 2H (benzylic methylene); 1.29, d, J = 6.5 cps, 3H (C-3 methyl) and 0.88, d, J = 6.0 cps, 6H (isopropyl).

Preparation of p-Bromophenoxyacetone (25). The procedure used was according to Hurd and Perletz.[35] Potassium iodide (1.5 g, 0.009 moles) and chloroacetone (70.0 g, 0.75 moles) were dissolved in 65 ml of dry acetone and allowed to stand overnight. p-Bromophenol (92.0 g, 0.53 moles) and potassium carbonate (17.0 g, 0.125 moles) were added to 70 ml of dry acetone and the mixture was refluxed for one hour. One-fourth of the potassium iodide-chloroacetone mixture was added dropwise over a period of one hour and then the second portion of potassium carbonate (17.0 g, 0.125 moles) was added, followed by a second portion of potassium iodide-chloroacetone. This procedure was continued until all of the chloroacetone and a total of 68 g, 0.50 moles, of potassium carbonate had been added. Dry acetone was added as needed to keep the mixture mobile. The mixture was allowed to reflux for 18 hours, then was cooled and filtered. The solvent and excess chloroacetone were removed on a rotary evaporator under vacuum leaving a brown oil which was distilled. The fraction boiling at 109-114°/0.15 mm was collected (105.1 g) and recrystallized from ethanol-hexane to produce a white solid (93.7 g). A second recrystallization gave white plates (87.9 g, 73%), m.p. 47°. The IR spectrum (KBr) showed significant bands at 1728 cm^{-1} (carbonyl) and 1052 cm^{-1} (ether). The NMR spectrum ($CDCl_3$) exhibited signals at δ 2.19, s, 3H (CH_3-CO-); 4.49, s, 2H (-O-CH_2-CO-) and 7.05, $A_2'B_2'$, 4H (p-substituted aromatic).

Anal. Calcd. for $C_9H_9O_2Br$: C, 47.19; H, 3.96. Found: C, 47.53; H, 3.83.

Preparation of 3-Methyl-5-Bromobenzofuran (26).

p-Bromophenoxyacetone (15 g, 0.065 moles) was mixed with polyphosphoric acid (45 ml) at room temperature in a single-necked flask equipped with a 105° adapter attached to a bent vacuum adapter bearing a receiver cooled in an icewater bath. The system was evacuated to 0.5 mm Hg and immersed in an oil bath preheated to 200°. The pale yellow distillate, collected over a fifteen minute period, was a mixture of the benzofuran and starting material. Redistillation afforded the benzofuran as a colorless liquid boiling at 61-63°/0.15 mm (5.1 g, 37%). The IR spectrum (film) showed significant bands at 1590 and 784 cm^{-1} (aromatic) and 1086 cm^{-1} (ether). The NMR spectrum (CCl_4) exhibited signals at δ 1.97, d, J = 1.1 cps, 3H (C-3 methyl); 7.19, m, 3H (C-6 and C-7 aromatic and C-2 hydrogens) and 7.45, dd, J_m = 1.0 cps and J_p = 0.6 cps, 1H (C-4 aromatic hydrogens).

Anal. Calcd. for C_9H_7OBr: C, 51.21; H, 3.34. Found: C, 51.43; H, 3.47.

Preparation of Ethylene Ketal of Levulinaldehyde (29).

6-Methyl-hept-5-ene-2-one (50 g, 0.40 moles) and ethylene glycol (50 g, 0.81 moles) were dissolved in benzene (200 ml). p-Toluenesulfonic acid monohydrate (0.5 g) was added and the mixture was refluxed for 48 hours while removing water through a modified Dean-Stark separator. Hexane (200 ml) was added and the organic phase was washed with sodium bicarbonate and dried over potassium carbonate. After removal of the solvent

a very pale yellow oil remained (67 g, 99%). The IR spectrum (film) showed no carbonyl absorption but did exhibit a band at 1046 cm^{-1} (ether). The NMR spectrum (neat) showed signals at δ 5.13, finely split t, J = 7.0, 1.0, and 0.7 cps, 1H (vinyl hydrogen); 3.76, s, 4H ($-O-CH_2-CH_2-O-$); 1.64, d, J = 1.0 cps, 3H (vinyl methyl); 1.58, d, J = 0.7 cps, 3H (vinyl methyl) and 1.23, s, 3H (quaternary methyl). This product was used without further purification. The ketal (30 g, 0.18 moles) was ozonized at -80° in absolute ethanol (50 ml) in three equal portions. The combined solutions of products of ozonolysis were hydrogenated over 1 g of 5% palladium charcoal. After filtration and removal of the solvent on a rotary evaporator under vacuum, the very pale yellow oil was distilled. The distillate was collected at 68.5-69°/5.5 mm (7.74 g, 50%). The IR spectrum (film) showed significant bands at 2720 and 1720 cm^{-1} (aldehyde) and 1046 cm^{-1} (ether). The NMR spectrum (CCl_4) exhibited signals at δ 9.61, t, J = 1.6 cps, 1H (-CHO); 3.84, s, 4H ($-O-CH_2-CH_2-O-$); 2.41, m, 2H ($-CH_2-CO-$); 1.96, A_2 of A_2B_2, 2H ($-C-CH_2-C-$) and 1.24, s, 3H (quaternary methyl).

Preparation of Ethylene Ketal of 3-Methyl-5-(4'-oxo-1'-hydroxypentyl)benzofuran (30). The Grignard reagent was prepared by refluxing for four hours under nitrogen a mixture of 3-methyl-5-bromobenzofuran (4.979 g, 23.6 mmoles) and magnesium (0.623 g, 25.6 mmoles) in 50 ml of tetrahydrofuran. The reaction mixture was allowed to cool and the ethylene ketal of levulinaldehyde (3.544 g, 24.6 mmoles) dissolved in 50 ml of tetrahydrofuan was slowly added. After the reaction mixture had stirred at room temperature for four hours, saturated ammonium chloride

solution was added. The reaction mixture was extracted three times with ether (100 ml) and the organic phase was washed with water and sodium bicarbonate. After drying over sodium sulfate, the solvent was removed under vacuum on a rotary evaporator leaving a yellow oil (5.640 g). Chromatography on Florisil (500 g) in hexane gave 3-methylbenzofuran (0.614 g, 20%). Elution with hexane-benzene (19:1) gave a pale yellow oil (1.832 g, 28%) while the remainder of the sample was more polar. The IR spectrum (film) showed bands at 3440 cm^{-1} (hydroxyl) and 1082 and 1058 cm^{-1} (ether). The NMR spectrum ($CDCl_3$) exhibited signals at δ 7.10-7.52, m, 4H (aromatic and C-2 hydrogens); 4.75, t, J = 6 cps, 1H (C<u>H</u>-OH); 3.82, s, 4H ($-O-CH_2-CH_2-O-$); 2.17, d, J = 1.1 cps, 3H (C-3 methyl) and 1.27, s, 3H (quaternary methyl).

Preparation of 3-Methyl-5-(4'-oxopentyl)benzofuran (31). The above alcohol (1.832 g, 6.6 mmoles) was dissolved in ethyl acetate (50 ml) and was hydrogenated at atmospheric pressure over 300 mg of 5% palladium on charcoal. Hydrogenation was interrupted after the uptake of one molar equivalent of hydrogen which required six hours. The mixture was filtered and the solvent removed under vacuum leaving a yellow oil. Chromatography on silicic acid (100 g) in benzene-ethyl acetate (49:1) resulted in a very pale yellow oil (1.393 g, 97%). The IR spectrum (film) showed bands at 1715 cm^{-1} (carbonyl) and 1084 cm^{-1} (ether). The NMR spectrum (CCl_4) exhibited signals at δ 6.83-7.43, m, 4H (aromatic and C-2 hydrogens); 2.64, t, J = 7 cps, 2H (benzylic methylene); 2.16, d, J = 1.2 cps, 3H (C-3 methyl) and 1.97, s, 3H (methyl ketone).

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 76.80; H, 7.46.

Preparation of 3-Methyl-5-(4'-methyl-4'-hydroxypentyl)benzofuran (32). To a solution of methyl magnesium iodide, prepared in the normal manner from magnesium (0.510 g, 21 mmoles) and methyl iodide (10 g, 70 mmoles) in ether (50 ml), was added a solution of the above ketone (31) (1.123 g, 5.2 mmoles) dissolved in ether (50 ml). The reaction mixture was stirred at room temperature for three hours then 6N hydrochloric acid (50 ml) was added. The mixture was extracted twice with ether (50 ml) and the organic phase was washed with water and then sodium bicarbonate. After drying over sodium sulfate, the solvent was removed under vacuum on a rotary evaporator leaving a brown oil (1.203 g). Chromatography on Florisil (100 g) in hexane-benzene (2:3) gave the alcohol as a colorless oil (0.971 g, 80%). The IR spectrum (film) showed significant bands at 3395 cm^{-1} (hydroxyl) and 1084 cm^{-1} (ether). The NMR spectrum (CCl_4) exhibited signals at δ 6.87-7.38, m, 4H (aromatic and C-2 hydrogens); 2.63, t, J = 6.5 cps, 2H (benzylic methylene); 2.08, d, J = 1.1 cps, 3H (C-3 methyl) and 1.10, s, 6H (gem-dimethyl).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.76; H, 8.70.

Preparation of 3-Methyl-5-(4'-methyl-3'-pentenyl)benzofuran (22). A solution of the above alcohol (32) (0.928 g, 4.0 mmoles) in dry pyridine (12 ml) was cooled to -10° with an ice-methanol bath and phosphorus oxychloride (2 ml) was slowly added. Pyridine hydrochloride began to precipitate immediately. The reaction mixture was allowed to stand at room temperature for two hours, poured into ice-water and extracted three times with hexane (50 ml). The organic solution was washed with water,

1N hydrochloric acid, water and sodium bicarbonate. After drying over sodium sulfate, the solvent was removed under vacuum on a rotary evaporator leaving a pale yellow oil (0.696 g). The IR spectrum (film) of the crude mixture showed significant bands at 1086 cm^{-1} (ether), 878 cm^{-1} (terminal methylene) and 805 and 780 cm^{-1} (trisubstituted double bond). In addition to the usual signals due to aromatic and C-2hydrogens and the C-3 methyl, the NMR spectrum (neat) showed signals at δ 5.19, t, J = 6.5 cps, (vinyl hydrogen) due to the trisubstituted double bond isomer; 4.75, broad s, (terminal methylene) due to the terminal methylene isomer and 1.37, s, (gem-dimethyl) due to the cyclized products.

The mixture was chromatographed on silver nitrate impregnated silicic acid (150 g). Elution with hexane-benzene (19:1), fractions 24-40, gave the cyclic products, a colorless oil (49 mg, 5.7%). The IR spectrum (film) showed significant bands at 1090 and 1084 cm^{-1} (ethers). The NMR spectrum (CCl_4) showed signals at δ 7.01-7.36, m, 3H (aromatic and C-2 hydrogen); 2.85, t, J = 6 cps, 2H (benzylic methylene); 2.13, d, J = 1.2 cps, 3H (C-3 methyl) and 1.29, s, 6H (gem-dimethyl).

Elution with hexane-benzene (3:1), fractions 67-77 (50 ml each), gave the desired product, the trisubstituted isomer, n_D^{25} 1.5956 (428 mg, 50%). The IR spectrum (film) showed significant bands at 3020 and 1183 cm^{-1} (aromatic) and 1086 cm^{-1} (ether). The NMR spectrum (neat) exhibited signals at δ 7.29, dd, J_o = 8.2 cps and J_p = 0.6 cps, 1H (C-7 aromatic hydrogen); 7.22, dd, J_m = 1.8 cps and J_p = 0.6 cps, 1H (C-4 aromatic hydrogen); 7.11, q, J = 1.1 cps, 1H (C-2 hydrogen); 6.96, dd, J_o = 8.2 cps and J_m = 1.8 cps, 1H (C-6 aromatic hydrogen); 5.19 finely

split triplet, J = 6.5, 1.0 and 0.7 cps, 1H (vinyl hydrogen); 2.5, one-half of A_2B_2, 2H (benzylic methylene); 2.30, m, 2H (allylic methylene); 1.97, d, J = 1.1 cps, 3H (C-3 methyl); 1.64, d, J = 1.0 cps, 3H (vinyl methyl) and 1.50, d, J = 0.7 cps, 3H (vinyl methyl).

Continued elution with hexane-benzene (3:1), fractions 78-92, gave the terminal methylene isomer, a colorless oil (175 mg, 21%). The IR spectrum (film) showed significant bands at 3076, 1647, and 878 cm^{-1} (terminal methylene), 3020 and 1184 cm^{-1} (aromatic) and 1086 cm^{-1} (ether). The NMR spectrum (CCl_4) exhibited signals at δ 7.27, dd, J_o = 8.0 cps and J_p = 0.6 cps, 1H (C-7 aromatic hydrogen); 7.22, dd, J_m = 1.8 cps and J_p = 0.6 cps, 1H (C-4 aromatic hydrogen); 7.21, q, J = 1.1 cps, 1H (C-2 hydrogen); 6.90, dd, J_o = 8.0 cps and J_m = 1.8 cps, 1H (C-6 aromatic hydrogen); 4.70, narrow m, 2H (terminal methylene); 2.67, t, J = 7 cps, 2H (benzylic methylene); 2.13, d, J = 1.1 cps, 3H (C-3 methyl) and 1.60, narrow m, 3H (vinyl methyl). Total yield of the dehydration products was 652 mg, 76%.

Preparation of m-Bromophenoxyacetone (36). The procedure used was according to Hurd and Perletz.[35] Chloroacetone (40 g, 0.43 moles) and potassium iodide (1 g, 0.006 moles) were dissolved in dry acetone (40 ml) and allowed to stand overnight. A mixture of m-bromophenol (50 g, 0.29 moles) and potassium carbonate (9.4 g, 0.068 moles) in dry acetone (60 ml) was refluxed for one hour. One-fourth of the potassium iodide-chloroacetone mixture was added dropwise over a period of one hour and then a second portion of potassium carbonate (9.4 g, 0.068 moles) was added, followed by a second portion of the potassium iodide-chloroacetone

mixture. This procedure was continued until all of the chloroacetone and a total of 37.6 g, 0.272 moles of potassium carbonate had been added. Dry acetone was added as needed to keep the mixture mobile. The mixture was allowed to reflux for 18 hours, cooled and filtered. The solvent and excess chloroacetone were removed on a rotary evaporator under vacuum leaving a black oil which was distilled. The fraction collected at 93-98°/0.15 mm (51.3 g) was redistilled and a pale yellow oil (34.5 g, 57%) was collected at 95-97°/0.15 mm. The NMR spectrum ($CDCl_3$) showed signals at δ 6.67-7.18, m 4H (aromatic hydrogens); 4.49, s, 2H ($-O-CH_2-CO-$) and 2.17, s, 3H (methyl ketone).

Anal. Calcd. for $C_9H_9O_2Br$: C, 47.19; H, 3.96. Found: C, 47,45; H, 3.93.

Preparation of 3-Methyl-6-Bromobenzofuran (38). m-Bromophenoxyacetone (39.1 g, 0.17 moles) was divided into three equal parts and was mixed with three portions of polyphosphoric acid (60 ml each) at room temperature in a single-necked flask equipped with a 105° adapter attached to a bent vacuum adapter bearing a receiver cooled in an ice-water bath. The system was evacuated to 0.5 mm Hg and immersed in an oil bath preheated to 200°. The three distillates, collected over a fifteen minute period, were a mixture of the two benzofurans and starting material (32.2 g). Redistillation afforded a mixture of 3-methyl-6 and 3-methyl-4-bromobenzofuran as a colorless oil boiling at 59-61°/0.2 mm (18.9 g, 53%).

Distillation through a Nester/Faust annular teflon spinning band column rated at 125 theoretical plates afforded several fractions.

Fractions 1-11, 54-55°/ 0.2 mm, were 95% pure 3-methyl-4-bromobenzofuran (17.02 g). Fractions 12-14, 56-58°/0.2 mm, and the pot residue (filtered through Florisil to remove oxidation products) were 95% pure 3-methyl-6-bromobenzofuran (6.57 g). Redistillation of fractions 1-11 at 52°/0.16 mm gave essentially pure (> 99%) 3-methyl- 4-bromobenzofuran (12.59 g) and the mixture (3.13 g). The IR spectrum (film) exhibited significant bands at 3120, 1568, and 895 cm^{-1} (aromatic) and 1100 cm^{-1} (ether). A first order interpretation of the aromatic region of the NMR spectrum (neat) did not fully explain all signals. Extra signals were explained as secondary splitting, thus the J values are only the apparent J values. Signals appeared at δ 7.17, dd, J_o = 7.8 cps and J_m = 1.4 cps, 1H (C-5 or C-7 aromatic hydrogen); 7.12, dd, J_o = 8.2 cps and J_m = 1.4 cps, 1H (C-5 or C-7 aromatic hydrogen); 7.03, dq, J = 1.1 and 0.4 cps, 1H (C-2 hydrogen); 6.77, ddd, J_o = 8.2 cps and J_o = 7.8 cps and J = 0.4 cps, 1H (C-6 aromatic hydrogen) and 2.14, d, J = 1.1 cps, 3H (C-3 methyl).

Anal. Calcd. for C_9H_7OBr: C, 51.21; H, 3.34. Found: C, 50.60; H, 3.43.

Chromatography on silicic acid (1000 g) in hexane of the distillation fractions 12-14 and the pot residue afforded essentially pure (> 99%) 3-methyl-6-bromobenzofuran (5.05 g) and the mixture (0.673 g). The IR spectrum (film) exhibited significant bands at 3120, 1572, 872, and 801 cm^{-1} (aromatic) and 1084 cm^{-1} (ether). The NMR spectrum (neat) showed signals at δ 7.38, dd, J_m = 1.6 cps and J_p = 0.5 cps, 1H (C-7 aromatic hydrogen); 7.10, dd, J_o = 8.2 cps and J_m = 1.6 cps,

1H (C-5 aromatic hydrogen); 7.06, q, J = 1.1 cps, 1H (C-2 hydrogen); 6.84, dd, J_o = 8.2 cps and J_p = 0.5 cps, 1H (C-4 aromatic hydrogen) and 1.86, d, J = 1.1 cps, 3H (C-3 methyl).

Anal. Calcd. for C_9H_7OBr: C, 51.21; H, 3.34. Found: C, 50.63; H, 3.36.

Preparation of the Ethylene Ketal of 3-Methyl-6-(4'-oxo-1'-hydroxypentyl)benzofuran (39). The Grignard reagent was prepared by refluxing for four hours under nitrogen a mixture of 3-methyl-6-bromobenzofuran (5.05 g, 23.9 mmoles) and magnesium (0.707 g, 29.1 mmoles) in tetrahydrofuran (50 ml). The reaction mixture was allowed to cool and the ethylene ketal of levulinaldehyde (3.809 g, 26.4 mmoles) was added slowly. After stirring at room temperature for four hours, saturated ammonium chloride was added. The reaction mixture was extracted three times with ether (100 ml) and the organic phase was washed with water and sodium bicarbonate. After drying over sodium sulfate, the solvent was removed under vacuum on a rotary evaporator leaving a yellow oil (5.687 g). Chromatography on Florisil (750 g) in benzene gave fractions 6-10, 3-methylbenzofuran (494 mg). Fractions 27-46, benzene-ethyl acetate (19:1), contained a mixture of several compounds (547 mg). Fractions 48-59, benzene-ethyl acetate (3:1), contained the alcohol as a pale yellow oil (2.682 g, 41%). The remainder of the sample was more polar material. The IR spectrum (film) showed significant bands at 3445 cm^{-1} (hydroxyl) and 1082 and 1055 cm^{-1} (ether). The NMR spectrum (CCl_4) showed signals at δ 6.97-7.42, m, 4H (aromatic and C-2 hydrogens); 4.62, t, J = 6 cps, 1H (-CH-OH); 3.73, s, 4H (-O-CH_2-CH_2-O-); 2.17, d, J = 1.1 cps, 3H (C-3 methyl) and 1.18, s, 3H (quaternary methyl).

Preparation of 3-Methyl-6-(4'-oxopentyl)-2,3-dihydrobenzofuran (40). The above alcohol (39) (2.682 g, 9.7 mmoles) was dissolved in ethyl acetate (50 ml) and hydrogenated over 5% palladium on charcoal (300 mg). The hydrogenation was interrupted after the uptake of one molar equivalent of hydrogen (24 hours). The mixture was filtered and the filtrate concentrated in vacuo to give a yellow oil (2.681 g). The NMR spectrum (CCl_4) of the crude oil showed signals at δ 6.70-7.41, m, 3H (aromatic hydrogens); 4.65, t, J = 6.5 cps, (-CH-OH); 4.57, dd, J = 8.5 and 7.5 cps, 1H (C-2 hydrogen); 3.98, dd, J = 7.5 and 7.0 cps, 1H (C-2 hydrogen); 3.68, s, 4H ($-O-CH_2-CH_2-O-$); 3.38, m, J = 8.5 and 7.0 and 6.5 cps, 1H (C-3 hydrogen); 1.25, d, J = 6.5 cps, 3H (C-3 methyl) and 1.19, s, 3H (quaternary methyl). The alcohol was dissolved in acetic acid (50 ml) and hydrogenated over 5% palladium on charcoal (300 mg) for 8 hours. The mixture was filtered and the solvent removed under vacuum on a rotary evaporator leaving a brown oil (2.651 g). Chromatography on Florisil (100 g) in benzene gave a pale yellow oil (0.724 g, 34%). The remainder of the sample was more polar material. The IR spectrum (film) showed significant bands at 1717 cm^{-1} (carbonyl) and 1059 cm^{-1} (ether).

Preparation of 3-Methyl-6-(4'-oxopentyl)benzofuran (41). The procedure used was that of Zalkow.[55] The crude ketone (40) above (724 mg, 3.3 mmoles) was dehydrogenated by heating with 5% palladium on charcoal (300 mg) at 165-170° for four hours. The reaction mixture was taken up in ethyl acetate, filtered and the solvent removed under vacuum on a rotary evaporator. The resulting orange oil (686 mg) was chromatographed on Florisil (50 g) in benzene. The early fractions gave a very pale

yellow oil (465 mg, 65%) which showed a single spot on thin layer chromatography (R_f 0.48, benzene-ethyl acetate, 9:1, silicic acid). The IR spectrum (film) showed bands at 1717 cm^{-1} (carbonyl) and 1082 cm^{-1} (ether). The NMR spectrum (CCl_4) showed signals at δ 6.82-7.41, m, 4H (aromatic and C-2 hydrogens); 2.15, d, J = 1.1 cps, 3H (C-3 methyl) and 1.95, s, 3H (methyl ketone).

Preparation of 3-Methyl-6-(4'-methyl-4'-hydroxypentyl)benzofuran (42). To a solution of methyl magnesium iodide in ether (50 ml), prepared in the normal manner under nitrogen from magnesium (0.604 g, 24.8 mmoles) and methyl iodide (10 g, 70 mmoles), was added a solution of the above ketone (41) (465 mg, 2.1 mmoles) in ether (50 ml). The reaction mixture was allowed to stir at room temperature for four hours. After addition of saturated ammonium chloride (50 ml), the mixture was extracted twice with ether (50 ml). The organic phase was washed with sodium bicarbonate and dried over sodium sulfate. After removal of the solvent under vacuum on a rotary evaporator, a brown oil (495 mg) remained. Chromatography on Florisil (50 g) in hexane-benzene (2:3) gave the alcohol as a colorless oil (282 mg, 57%). The IR spectrum (film) showed bands at 3390 cm^{-1} (hydroxyl) and 1082 cm^{-1} (ether). The NMR spectrum ($CDCl_3$) showed signals at δ 6.91-7.47, m, 4H (aromatic and C-2 hydrogen); 2.33, t, J = 7 cps, 2H (benzylic methylene); 2.12, d, J = 1.1 cps, 3H (C-3 methyl) and 1.10, s, 6H (gem-dimethyl).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.41; H, 8.74.

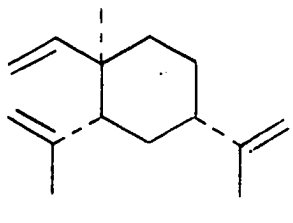
Preparation of 3-Methyl-6-(4'-methyl-3'-pentenyl)benzofuran (23). To a solution, cooled to -10° with an ice-methanol bath, of the above alcohol (42), (270 mg, 1.1 mmoles) in dry pyridine (6 ml) was very slowly added phosphorus oxychloride (1 ml). Pyridine hydrochloride began to precipitate immediately. The reaction mixture was allowed to warm to room temperature over two hours, was poured into ice-water and extracted three times with hexane (50 ml). The organic solution was washed with water, 1N hydrochloric acid, water and sodium bicarbonate and then dried over sodium sulfate. The solvent was removed under vacuum on a rotary evaporator leaving a pale yellow oil (155 mg). The IR spectrum (film) of the crude mixture showed significant bands at 1083 cm^{-1} (ether), 880 cm^{-1} (terminal methylene) and 805 and 785 cm^{-1} (trisubstituted double bond). In addition to the usual aromatic and C-3 methyl signals, the NMR spectrum (CCl_4) exhibited signals at δ 5.19, t, J = 6.5 cps (vinyl hydrogen) due to the trisubstituted double bond isomer; 4.75, broad s, (terminal methylene) due to the terminal methylene isomer and 1.37, s, (gem-dimethyl) due to the cyclized products. Preparative gas chromatography (20' x 3/8" 30% SE-30 on 45/60 Chromsorb P) separated the sample into two fractions. The first was a colorless oil (18 mg, 7%) not further characterized but presumably the cyclic products. The second fraction was a mixture of the trisubstituted and terminal methylene double bond isomer (104 mg). The IR spectrum (film) showed signals at 1083 cm^{-1} (ether), 880 cm^{-1} (terminal methylene), and 805 and 785 cm^{-1} (trisubstituted double bond). In addition to the usual aromatic and C-3 methyl signals, the NMR spectra (CCl_4) exhited signals

at δ 5.19, t, J = 6.5 cps, (vinyl hydrogen) and 4.75, broad s, (terminal methylene). The mixture was chromatographed on silver nitrate impregnated silicic acid (20 g) in hexane-benzene (49:1). The early fractions (5-19, 30 ml each) contained the trisubstituted isomer, 3-methyl-6-(4'-methyl-3'-pentenyl)benzofuran, a colorless oil (62 mg, 25%). The IR spectrum (film) exhibited bands at 3030 and 1129 cm^{-1} (aromatic), 1084 cm^{-1} (ether) and 808 and 796 cm^{-1} (trisubstituted double bond) and was identical in all respects to the IR spectrum of the naturally occurring compound. The NMR spectrum (neat) showed signals at δ 7.29, dd, J_o = 8.0 cps and J_p = 0.6 cps 1H (C-4 aromatic hydrogen); 7.25, dd, J_m = 1.2 cps and J_p = 0.6 cps, 1H (C-7 aromatic hydrogen; 7.13, q, J = 1.1 cps, 1H (C-2 hydrogen); 6.98, dd, J_o = 8.0 cps and J_m = 1.2 cps, 1H (C-5 aromatic hydrogen); 5.19, finely split t, J = 7.5, 1.0 and 0.7 cps, 1H (vinyl hydrogen); 2.51, A_2 of A_2B_2, 2H (benzylic methylene); 2.30, m, 2H (allylic methylene); 1.97, d, J = 1.1 cps, 3H (C-3 methyl); 1.64, d, J = 1.0 cps, 3H (cis vinyl methyl) and 1.50, d, J = 0.7 cps, 3H (trans vinyl methyl).

Elution with hexane-benzene (9:1) gave a pale yellow oil (23 mg, 9%) not further characterized but presumably the terminal methylene double bond isomer.

SUMMARY

Six sesquiterpene hydrocarbons have been isolated from three species of gorgonians. (+)-β-Elemene (1) was shown to be the major sesquiterpene hydrocarbon occurring in an aged sample of the pentane extract of Eunicea mammosa. Only one sesquiterpene hydrocarbon, (+)-β-ylangene



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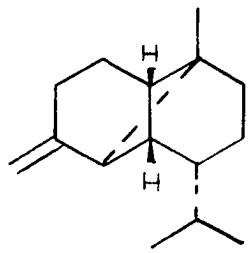

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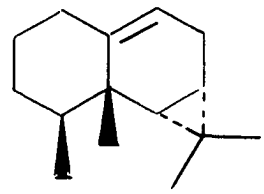

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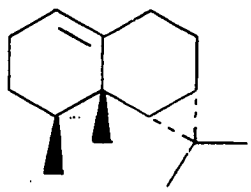

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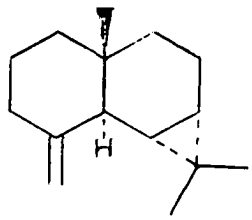

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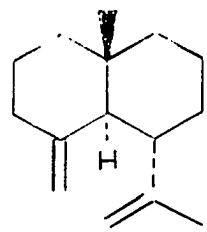


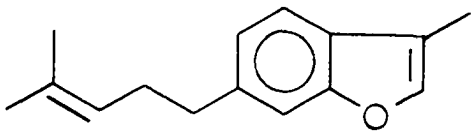
(8)

(4) was isolated in a pure state from Pseudoplexaura porosa. Several other hydrocarbons were also present but could not be separated from other. Four hydrocarbons were isolated from Pseudopterogorgia americana: (+)-9-aristolene (5), (-)-1(10)-aristolene (6), (+)-γ-maaliene (7), and (+)-β-gorgonene (8). These four comprised the bulk of the sesquiterpene

hydrocarbon fraction but several other hydrocarbons were also present in amounts less than 1% of the mixture. Four of the hydrocarbons, (+)-β-elemene (1), (+)-β-ylangene (4), (+)-9-aristolene (5) and (-)-1(10)-aristolene (6) were previously known and were identified by comparison of spectra and physical properties. (+)-γ-Maaliene (7) had not been previously encountered in nature but was characterized in the form of the diol which had been reported previously. (+)-β-Gorgonene (8) was shown by x-ray crystallography to be an unknown hydrocarbon with a new carbon skeleton.

It is interesting to note that in the four cases where it was possible to make a comparison, (+)-β-elemene (1), (+)-9-aristolene (5), (-)-1(10)-aristolene (6) and (+)-γ-maaliene (7), the hydrocarbons found in the marine organisms were the enantiomers of the more common form of the carbon skeletons found in terrestrial sources.

The structure of the sesquiterpenoid benzofuran, furanoventalinene (23), isolated from Gorgonia ventalina was deduced from the spectral data and confirmed by synthesis as 3-methyl-6-(4'-methyl-3'-pentenyl)benzofuran.



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